National Library of Canada
Bibliothèque nationale du Canada

Canadian Theses Service
Service des thèses canadiennes

Ottawa, Canada
K1A 0N4

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, tests publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30.

NL-339 (r. 88/04)

Canada

THE UNIVERSITY OF ALBERTA

INTRATHECAL NIMODIPINE THERAPY IN A PRIMATE MODEL OF CHRONIC CEREBRAL VASOSPASM

BY

Paul Jeffrey Lewis

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

IN EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

FALL 1987

Permission has been granted to the National Library of Canada to microfilm this thesis and to lend or sell copies of the film.

The author (copyright owner) has reserved other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without his/her written permission.

L'autorisation a été accordée à la Bibliothèque nationale du Canada de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur (titulaire du droit d'auteur) se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation écrite.

ISBN 0-315-40940-1

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: Paul Jeffrey Lewis

TITLE OF THESIS: Intrathecal Nimodipine Therapy
in a Primate Model of
Chronic Cerebral Vasospasm

DEGREE: Master of Science

YEAR THIS DEGREE GRANTED: 1987

Permission is hereby granted to the UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

P.J. Lewis

.....

P. Jeffrey Lewis, M.D.
Division of Neurosurgery
8440 112 Street
2D3.74 WMC
University of Alberta
Edmonton, Alberta
T6G 2B7

May 26, 1987

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled INTRATHECAL NIMODIPINE THERAPY IN A PRIMATE MODEL OF CHRONIC CEREBRAL VASOSPASM submitted by Paul Jeffrey Lewis in partial fulfilment of the requirements for the degree of Master of Science in Experimental Surgery.

.....
B.K.A. Weir, M.D., supervisor

.....
D.A. Cook, M.A., D.Phil.

.....
T.R. Overton, Ph.D.

.....
M.G.A. Grace, Ph.D.

.....
J.D.R. Miller, M.D.

ABSTRACT

The safety, prevention, and treatment of chronic vasospasm by repeated administration of intrathecally applied nimodipine was evaluated in a primate model of chronic cerebral vasospasm. Twenty-four female cynomolgous monkeys were randomized into 3 groups of 8: 1) sham 2) clot and 3) clot + intrathecal nimodipine. All animals underwent bilateral craniectomies and microsurgical arachnoid dissection, following baseline angiography. An average of 8 ml of autologous blood clot was placed bilaterally over the major cerebral arteries in all animals except the sham group. Nimodipine was administered postoperatively by percutaneous injection of 1 ml (0.2mg) tid for 6 days, through an Ommaya reservoir with the catheter placed in the subarachnoid basal cisterns. The safety of nimodipine applied in this way and it's effect on prevention of delayed ischemic neurological deficits and angiographic vasospasm was evaluated by neurological assessment, repeat angiography at day 7 post-SAH induction, and brain pathological examination. The effect of intrathecally applied nimodipine on dilation of normal and vasospastic vessels in vivo, was evaluated by angio-

graphy following an injection of 1 ml (0.2 mg) of nimodipine into the Ommaya reservoir at day 7 in all animals. The diffusion of intrathecal nimodipine through the CSF when administered via the Ommaya reservoir was assessed indirectly using horseradish peroxidase (HRP) as a marker. The HRP was administered intrathecally, 15 min prior to sacrifice. The vessels were then studied by scanning and transmission electron microscopy.

Intrathecally applied nimodipine was not found to be effective in prevention of angiographic vasospasm. It also did not appear to decrease the degree of pathological change when compared to controls. No adverse pathological effects were noted from the intrathecal administration of nimodipine, however transient sedation and hypoventilation were common. Since no animal developed a delayed ischemic neurological deficit in any of the groups, nimodipine's role in preventing delayed ischemic neurological deficits could not be assessed. Intrathecal nimodipine was not found to produce a significant dilation of vessels in moderate or severe spasm when assessed by angiography 2 hours following a single intrathecal injection. However, dilation of vessels in mild spasm

which were not covered by subarachnoid clot (eg. basilar artery) did occur after an intrathecal nimodipine injection. When administered through the Ommaya reservoir, the HRP stained the circle of Willis diffusely brown in all animals.

Key words: chronic vasospasm. intrathecal nimodipine. primate model

PREFACE

Aneurysmal subarachnoid hemorrhage is one of the most devastating tragedies inflicted on a human being. Eighteen thousand people die or become permanently disabled each year in North America. Many are in the most productive years of their life. Thirty years ago, operative mortality in a patient fortunate enough to survive the initial insult and obtain neurosurgical care was 80 %. Great advances have been made in cerebral aneurysm surgery with the aid of the operating microscope and micro-instrumentation. The operative mortality for aneurysm surgery is now under 10 %. Neurosurgeons are now able to effectively obliterate an aneurysm from the cerebral circulation and prevent recurrent hemorrhage. Cerebral vasospasm is now the leading cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage. The advances in vasospasm therapy have not been as impressive, however progess is taking place.

An exciting development in cerebral vasospasm research involves the use of a reliable, reproducible primate model of chronic vasospasm which has been developed in the Cerebrovascular Research Laboratory at the University of Alberta. Research on this animal

model has provided a gold standard for evaluation of various treatment modalities.

The work presented in this thesis is an extension of Dr. F. Espinosa's and Dr. M. Nosko's work on therapy for chronic vasospasm in the primate model using the calcium antagonist nimodipine. It is hoped that this work will help clarify the literature concerning intrathecal administration of nimodipine and aid in effective progess toward a solution to this frustrating problem of cerebral vasospasm.

ACKOWLEDGEMENTS

Dr. Bryce Weir has provided an exceptional opportunity for a neurosurgery resident to be a part of his renowned research. I am grateful for the hours of microsurgical training which I received in his cerebrovascular laboratory. The training that I received will be the basis for a career in microneurosurgery. I would like to express my appreciation to Dr. Weir for his academic influence and guidance during this research year and throughout my neurosurgery residency.

I would like to thank Dr. Michael Nosko for our many discussions and his advice on the practical aspects of the cerebrovascular laboratory and graduate study research. His previous work in the laboratory facilitated my research study and helped make this research year successful.

I would also like to thank Dr. Michael Grace for his guidance on statistical analysis and graduate study research; and Drs. Thomas Overton, David Cook and Jack Miller for their review and criticisms of the thesis.

Excellent technical assistance was provided by Mrs. T. Gorodetski who maintained the laboratory in a functional state throughout the year. Mr. G. Hawkins provided the gentle care and attention to the animals

in the vivarium which allows this essential research to continue. I would also like to thank Mrs. E. Schwaldt for her technical assistance in the preparation of specimens for electron microscopy and Dr. V. Manikavel for his advice on HRP immunochemistry.

Dr. A. Scriabine of Miles Laboratories provided the nimodipine for the study.

This study was supported by grants from the Medical Research Council of Canada.

I am grateful to the Alberta Heritage Foundation for Medical Research for providing me with a Research Fellowship.

TABLE OF CONTENTS

page

CHAPTER ONE: CHRONIC CEREBRAL VASOSPASM
REVIEW OF THE LITERATURE

Introduction 1

Incidence 3

Diagnosis 5

Pathophysiology 9

Experimental In Vivo
Animal Models 11

Pathology 16

Etiology 24

Treatment 40

Summary 63

CHAPTER TWO: THE PRESENT STUDY

Objectives 65

MATERIALS AND METHODS

Randomization 66

Baseline Angiography 66

SAH Induction 68

Intrathecal Nimodipine
Administration 74

page

Day 7 - Angiography 75

Sacrifice 75

Data Measurements and Analysis 76

CHAPTER THREE: RESULTS

Neurological Status 78

Prevention of Angiographic Vasospasm 80

Treatment of Chronic Vasospasm 85

Pathology 91

CHAPTER FOUR: DISCUSSION 97

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS 102

BIBLIOGRAPHY 106

PUBLICATIONS 128

LIST OF TABLES

Table page

1. Measurements of Physiological Parameters and Angiographic Vessel Caliber 79

2. Severity of Vasospasm in Control and Treatment Groups 83

LIST OF FIGURES

Figure		page
1.	Arachnoid Dissection of Basal Cisterns	71
2.	Induction of Subarachnoid Hemorrhage	72
3.	Insertion of Ommaya Reservoir	73
4.	Bar Graph of Percentage Change in Vessel Caliber from Baseline	82
5.	Cerebral Angiograms of Baseline, Control, and Treatment Groups	84
6.	Line Graph of Change in Vessel Caliber after Intrathecal Nimodipine	87
7.	Cerebral Angiograms at Baseline and Day 7 Before and After Intrathecal Nimodipine	88
8.	Cerebral Angiograms at Baseline and Day 7 Before and After Intrathecal Nimodipine	89
9.	Cerebral Angiograms at Day 7 Before and After Intrathecal Nimodipine	90
10.	Cerebral Vessel Staining by HRP	92
11.	Scanning Electron Microscopy of Control and Treatment Groups	93
12.	Light Microscopy of Sham and Nimodipine Groups	94
13.	Light Microscopy of Sham and Nimodipine Groups	95
14.	Transmission Electron Microscopy of Sham and Nimodipine Groups	96

CHAPTER ONE: CHRONIC CEREBRAL VASOSPASM

REVIEW OF THE LITERATURE

INTRODUCTION

Chronic cerebral vasospasm is presently the leading cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage, in patients who reach neurosurgical referral centres (84). Over the past 20 years, extensive research has been devoted to this very difficult clinical problem. Great advances in understanding the pathogenesis have been made, however a consistently effective method of therapy has not yet been developed (195).

Chronic cerebral vasospasm is recognized as a reversible constriction of cerebral vessels of a diffuse or focal nature, in response to perivascular blood in the subarachnoid space. The constriction appears to involve morphological changes in the vessel wall acting in concert with sustained vascular smooth muscle contraction (33,45,85,91).

Robertson (143) in 1949 first reported on ischemic lesions in patients with ruptured intracranial aneurysms and concluded that these lesions were occasionally due to arterial spasm. In 1951, Poppen (140) noted cerebral

arterial spasm at surgery for rupture of an aneurysm. Trauma to the arterial wall from perivascular extravasation of blood was considered to be the cause of the spasm. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage was first demonstrated angiographically by Ecker and Riemenschneider (38) in 1951. They noted angiographic narrowing of the larger intracranial arteries in 10 patients, 6 of whom harboured a saccular arterial aneurysm of the circle of Willis. Other instances of spasm were associated with: ligation of the cervical carotid artery, astrocytoma, intracerebral hemorrhage and a severe intrinsic lesion of the arteries. They postulated that the common element seemed to be abrupt traction on the arterial wall.

It is well recognized today that cerebral vasospasm most commonly follows subarachnoid hemorrhage from rupture of a cerebral aneurysm and has been reported to be infrequently associated with head trauma, rupture of arteriovenous malformations, pituitary apoplexy, hypothalamic-pituitary surgery, meningitis, migraine and surgery for unruptured intracranial aneurysms (13,27,28,49,78,101,102,107,135,142,153).

INCIDENCE

Autopsy studies have estimated that as many as 5 million people in North America may harbour an intracranial aneurysm (110). Approximately 28,000 aneurysms will rupture each year (81). This incidence has remained remarkably constant over many years (1,139). Of the 28,000 aneurysms that rupture, approximately 10,000 patients will die or become disabled after the initial insult before receiving definite neurosurgical care. About 18,000 patients will be referred to neurosurgical centres each year. Of these patients, approximately 8,000 will die or become disabled; 3,000 from rebleeding, 3,000 from vasospasm, 1,000 from medical complications, and 1,000 from surgical complications. This leaves 10,000 functional survivors each year. The overall mortality and morbidity rate is 64 %. About 17 % of patients referred to a neurosurgical centre will die or become disabled from cerebral vasospasm (83,99).

The incidence of angiographically demonstrated vasospasm has been reported to be between 40 - 70 % (6,56,148). Allcock and Drake (6) reported the incidence of angiographic vasospasm to be 45 % at less

than 3 days after subarachnoid hemorrhage, 41 % at 3 to 10 days, and 25 % at more than 10 days. Usually, the onset of vasospasm occurs about the third day following subarachnoid hemorrhage, is maximal about the sixth to eighth day and disappears by about the twelfth day (186). However, reports exist of vasospasm persisting for as long as 5 weeks after subarachnoid hemorrhage (18). The possibility of rebleeding must be considered in cases of prolonged persistance of vasospasm (186).

Delayed ischemic neurological deficits from vasospasm after aneurysmal subarachnoid hemorrhage occurs in 20 - 37 % of patients, resulting in death or permanent neurological disability in about 7 - 20 % (7,73,83,141,145).

DIAGNOSIS

The clinical manifestations of cerebral vasospasm usually begin between 4 and 12 days after subarachnoid hemorrhage with a delay of 6 hours to 3 days after the onset of angiographic vasospasm. The rate of development of the neurological deficits is insidious over a period of hours to a few days. Frequently, an increase in headache and a low-grade fever precede neurological signs. Rousseaux et al. (147) reported this delayed fever in 88.3 % of patients who had aneurysms with severe angiographic vasospasm and delayed ischemic signs. They suggested that the delayed fever is not a simple sign of a meningeal syndrome but related to cerebral vasospasm. An early disturbance of consciousness usually then precedes focal neurological signs. A fluctuating clinical course is not uncommon with gradual resolution or progression to a major focal deficit. Occasionally, relentless progression to coma and decerebration occurs within hours. Disturbances of sensorium are common with anterior cerebral artery vasospasm and disturbances of conciousness with posterior circulation or diffuse vasospasm. Focal neurological deficits are more common with middle cerebral arterial spasm (52,73).

The differential diagnosis of delayed deterioration after aneurysmal subarachnoid hemorrhage is multifactorial. Peerless (136) reported a 30 % incidence of delayed deterioration from vasospasm, 6 % from rebleeding, 14 % from hydrocephalus, and 18 % from hyponatremia. Many medical complications also contributed to delayed neurological deterioration.

Associated risk factors may precipitate or aggravate symptomatic vasospasm. Hypovolemia is an important correctable risk factor. Maroon and Nelson (105) found a significantly decreased red blood cell mass and total blood volume in 15 nonselected patients with subarachnoid hemorrhage. Kudo et al. (92) measured circulating blood volume with an isotope dilution technique and found a decreased blood volume and red blood cell mass at the time of neurological deterioration in 3 patients with vasospasm. Rosenwasser et al. (146) reported a 20 % incidence of angiographic vasospasm in patients treated with preoperative volume expansion and vasodilator/centrally acting drugs for control of hypertension compared to a 60 % incidence of vasospasm in a group of patients treated with diuretics for preoperative control of hypertension. Systemic arterial hypotension and increased intracranial pressure

may also result in reduced cerebral perfusion pressure when autoregulation is impaired after subarachnoid hemorrhage, thus increasing the risk of vasospasm (26,47,48,90,116). Hydrocephalus and antifibrinolytic therapy have also been noted to have an increased association with symptomatic vasospasm (19,57,88,159).

From the above, it is evident that delayed clinical deterioration after aneurysmal subarachnoid hemorrhage must be evaluated carefully with clinical examination, blood chemistry and CT scanning. Angiography is indicated if the diagnosis is unclear. When angiographic narrowing is demonstrated, multifactorial causation may also be present.

The most useful predictor of the severity of vasospasm and subsesquent cerebral infarction is the size of the subarachnoid hematoma on CT scans and the presence of basal subarachnoid contrast enhancement (34,74,89,115,168,178). Mizukami et al. (115) noted that the presence of thick subarachnoid hematoma characterized by high density on CT scans (Hounsfield number greater than 60) within 4 days of subarachnoid hemorrhage was associated with an 84.6 % incidence of cerebral vasospasm. Tazawa et al. (178) reported a 46 % incidence of prominent contrast enhancement in the

region of the circle of Willis on CT scans between day 0 and day 3 after subarachnoid hemorrhage. Severe vasospasm with motor paralysis occurred in 76 % of these patients. Hirata et al. (74) found that the diffuse type of subarachnoid enhancement on CT scan was most valuable for predicting cerebral infarction due to vasospasm (83% of patients developed cerebral infarction). Doczi et al. (34) suggested that the abnormal enhancement is parenchymal, in the gyri, and not subarachnoid. They postulated that it is due to gyral hyperemia or extravasation of contrast material into cortex resulting from breakdown of the blood-brain barrier.

PATHOPHYSIOLOGY

Approximately 50 % of patients with angiographic cerebral arterial narrowing do not develop symptoms of cerebral ischemia. However, there is ample evidence showing a positive correlation of severe angiographic vasospasm (greater than one-third reduction of vessel caliber) with reduced cerebral blood flow, delayed ischemic neurological deficits, pathological cerebral infarction and poor outcome (33,62,64,77,106,112,196). Ishii (77) demonstrated focal areas of decreased cerebral blood flow below 30 ml/100 gm/min in all patients with diffuse, severe vasospasm (greater than 50 % reduction of vessel caliber). These patients also demonstrated impaired CO_2 response and autoregulation, as well as severe neurological deficits. Graham et al. (62) found ischemic damage in the cerebral cortex of 88 % of hemispheres with severe vasospasm. Martin et al. (106), using positron emission tomography demonstrated a reduction of cerebral blood flow and oxygen utilization in all patients with subarachnoid hemorrhage, with the most pronounced reductions in patients with more severe neurological deficits and severe vasospasm. Their most striking finding was a significant increase in cerebral blood volume in those

patients with severe neurological deficits associated with severe vasospasm. They suggested that cerebral vasospasm consists of constriction of the large, radiographically visible extraparenchymal vessels accompanied by a massive dilation of intraparenchymal vessels in response to cerebral ischemic cellular metabolites. The increased blood volume and ischemic cerebral edema elevate intracranial pressure which further reduces perfusion pressure and cerebral blood flow, in the presence of the impaired autoregulation of subarachnoid hemorrhage. These abnormalities may ultimately lead to cerebral infarction.

EXPERIMENTAL IN VIVO ANIMAL MODELS

An understanding of the pathology, etiology, pathogenesis and results of various treatment modalities on cerebral vasospasm has been obtained from the research on experimental in vivo animal models of subarachnoid hemorrhage. A good animal model should ideally produce angiographic vessel narrowing with a delayed onset and prolonged duration of existence which simulates the time course of clinical chronic cerebral vasospasm. The model should also produce delayed ischemic neurological deficits from the vasospasm to further approximate the clinical situation. Low cost and availability of the experimental animals would be an additional desirable feature. Species variation of the cerebral vessels to various etiological substances and pharmacological treatment modalities must also be considered.

Echlin (37) in 1964 performed a transclival surgical approach on monkeys and applied fresh autologous blood on the vertebral and basilar arteries for 1/2 to 5 minutes to produce vasospasm. Photomicrographs were used to document the vasospasm. The onset of vasospasm was immediate and lasted for 5 to 10 minutes. Echlin observed the need for the arachnoid to

e dissected and the blood placed in the subarachnoid pace in order to achieve vasospasm. However, the time ourse of this acute spasm is very different than that f chronic vasospasm in the clinical situation. Simeone t al. (163) in 1968 produced prolonged vasospasm in esus monkeys by puncture of a major vessel in the ircle of Willis. The vasospasm was studied ngiographically and persisted throughout the duration f the experiment, lasting over 4 days and limited ually by survival of the animals. The main difficulty th this model was the high mortality rate. Also, cause of the inability to control the amount of morrhage following arterial puncture, the degree of sospasm produced was highly variable between animals.

Recent development of a primate model in nomolgous monkeys is one of the superior present y models (41,42,43). This model involves performing a ilateral frontotemporal craniectomy and the placement f autologous blood clot in the subarachnoid space after achnoid dissection and exposure of the internal rotid, middle cerebral and anterior cerebral arteries. e mortality from the procedure is low with an 87 % cidence of vasospasm. The vasospasm is delayed in set, maximizes at day 7 after subarachnoid hemorrhage

induction and decreases by day 14, a time course very similiar to clinical vasospasm (43,186). The incidence and severity of the vasospasm were related to the size of the hemorrhage. However, the incidence of delayed neurological deficit was only about 6 to 10 %. Nosko and Weir (120) extended this model to a bilateral craniectomy and clot placement over the anterior and posterior circulation vessels bilaterally, in order to reduce collateral blood flow. The incidence of delayed neurological deficit was 25 %, an incidence which approximates the clinical situation more closely (73,141,145). The severity of vasospasm was also increased with significant vasospasm (greater that 25 % reduction of vessel caliber) occurring in all non-treatment control animals.

Species variation of cerebral vessel response to vasogenic substances such as hemoglobin, norepinephrine, and thromboxane A_2 has been reported (69,151,177,180, 188). The similarities of monkey and human cerebral vessels have been consistently verified in these studies. Cerebral arteries from dog, cat, rat, rabbit, and pig specimens have shown significant difference in vasogenic response in comparison to monkey and human vessels. However, in view of low cost, availability,

and ease of handling animals, models of vasospasm with mammals other than monkeys have been extensively used (4,17,32,60,108,182,201).

The two-hemorrhage canine model recently has been very popular and is reported to mimic the vasospasm seen in patients with subarachnoid hemorrhage because it is so refractory to pharmacological therapy (60,182,201). Subarachnoid hemorrhage is induced by injection of 4 ml of fresh unheparinized arterial blood into the cisterna magna and this is followed by a second injection 48 hours later. Zabramski et al. (201) have extended this model to three injections, each 24 hours apart. Their three-hemorrhage model, using a total of 15 ml of blood produced a 58 % reduction in basilar artery caliber compared to a 37 % reduction in a two-hemorrhage control group (9 ml of blood). The spasm resolved over approximately 3 weeks. They have developed a technically simple protocol for the reliable production of severe chronic vasospasm. However, the presence of delayed neurological deficits was not reported.

The bilateral craniectomy primate model must be considered to be the best model of chronic cerebral vasospasm in terms of severity and time course of angiographic vasospasm, production of delayed ischemic

neurological deficits, and blood vessel similarity to human cerebral vessels. The disadvantages include: expense, low availability, and difficulty in handling monkeys.

PATHOLOGY

Morphological changes in the cerebral blood vessels of patients dying of subarachnoid hemorrhage were first described by Crompton (33) in 1964. He reported the presence of degeneration and necrosis of blood vessels within large subarachnoid hematomata and stasis of blood flow through these vessels, contributing to the occurrence of cerebral infarction. Conway and McDonald (32) studied the intradural arteries of 12 autopsy cases of subarachnoid hemorrhage. In all patients surviving 4 weeks or more, the lumina of the intracranial arteries were narrowed by subendothelial granulation tissue which thickened the intima. The changes were restricted to large arteries with a prominent muscular layer and confined to the subarachnoid space. The presence and degree of intimal thickening correlated with the distribution and amount of subarachnoid blood. Hughes and Schianchi (76) also noted concentric intimal thickening by subendothelial fibrosis located in vessels formerly in spasm, in patients surviving 3 weeks or more. These late changes were distinguished from early cases where the most significant abnormality was necrosis in the tunica media. Other early changes noted

were intimal swelling, corrugation of the tunica elastica, and adventitial infiltration by lymphocytes, plasma cells and macrophages. Other late changes noted were atrophy of the tunica media which was associated with dilation of the arterial lumen on angiography (114).

Pathological studies in experimental models of subarachnoid hemorrhage have provided more detail than human autopsy specimens through the use of perfusion fixation and electron microscopy. Excellent descriptions of the vascular ultrastructure in experimental models of cerbral vasospasm are provided by Fein et al. (50), Espinosa et al. (45) and Zervas et al. (204).

The ultrastructure of a normal cerebral artery shows a single layer of spindle-shaped endothelial cells lining the lumen and joined by tight junctions, forming the blood-arterial wall barrier. The elastic lamina separates the endothelium from the smooth muscle layer. The smooth muscle cells are spindle-shaped and contain a central core of cellular organelles, and an elongated nucleus surrounded by muscle filaments. A basement membrane coats these cells and the intercellular space contains collagen fibers. The adventitia is composed of

adventitial cells that form a distinct cell surface on which stomata and arachnoid trabeculae are identified. The adventitial cells are separated by gap junctions or open spaces. Collagen bundles form a much less dense framework in the adventitia of cerebral vessels compared to systemic vessels. Vasa vasorum are absent in cerebral vessel adventitia. Zervas et al. (204) identified a labyrinthine structure or rete vasorum which allows morphological communication of CSF with the smooth-muscle cells of the media and may provide a pathway in the adventitia for nourishment of cerebral vessels, analogous to systemic vasa vasorum.

Fein et al. (50) studied the sequential vascular changes of cerebral vasospasm using a primate model. Early spasm was produced angiographically by the intracisternal injection of 3 ml of arterial blood with angiography performed 20 minutes to 1 hour after the subarachnoid hemorrhage induction. This acute spasm is very rarely seen clinically (186). The light microscopy changes showed a reduction in lumen size with corrugation of the internal elastica which was indistinguishable from normally constricted arteries. However, electron microscopy revealed structural changes only in the media characterized by condensed lysosomes

and degenerating mitochondria. Prolonged spasm of 2 to 7 days was produced by needle puncture of the intradural internal carotid artery. The ultrastructural changes consisted of desquamated endothelial cells with loss of tight junctions and platelet adherence to the denuded elastica. Adjacent smooth muscle cells showed evidence of myonecrosis with large intracellular vacuoles. Espinosa et al. (45) visualized the ultrastructural abnormalities in a primate model of chronic vasospasm at day 14 post-subarachnoid hemorrhage induction when angiographic vasospasm had almost completely abated. They showed dramatic changes using scanning and transmission electron microscopy. There was convolution of the endothelial surface, thickening of the arterial wall and absence of nerves on the adventitia as seen by scanning electron microscopy. Transmission electron micrographs showed endothelial swelling, vacuolization, rounding, and disruption of tight junctions. Migration of smooth muscle cells to the subendothelial space, thinning of the internal elastic lamina, convolution of the intima and elastic lamina, and vacuolization with fibrosis of the media were also identified. There was minimal inflammatory reaction in the adventitia. The authors believe that

vasospasm is due to long-lasting smooth muscle contraction and not to a proliferative vasculopathy, since the above described morphological changes were present when angiographic spasm had almost completely abated.

Sasaki et al. (151,152) have studied vascular permeability after experimental subarachnoid hemorrhage in the acute and chronic stage. Acutely, after 30 minutes of an intracisternal injection of either mock CSF or whole arterial blood in a rat model, horseradish peroxidase (HRP) reactive products permeated into the subendothelial space and the smooth muscle layer. Control animals showed HRP reaction products in luminal pits and in intracellular plasmalemmal vesicles of endothelial cells, but no permeation of HRP reaction products into the subendothelial space. Five hours after the intracisternal injection, no permeability abnormalities were noted. A transient rise in intracranial pressure and systemic arterial pressure after an intracisternal injection of mock CSF or blood was noted. The authors postulate that a sudden rise in arterial blood pressure after the increase in intracranial pressure resulted in the transiently increased permeability of the major cerebral arteries.

Endothelial cell transcytosis was the important mechanism for the enhanced permeability, rather than the opening of interendothelial tight junctions. However, in a chronic canine model of vasospasm, Sasaki et al. (151) demonstrated extensive disturbance in the blood-arterial wall barrier of the major cerebral arteries after subarachnoid hemorrhage, with or without elevation of intracranial pressure. Opening of the inter-endothelial tight junctions was the major mechanism for HRP leakage into the subendothelial space and the smooth muscle layer. The disturbance in arterial permeability of the major cerebral arteries after subarachnoid hemorrhage may account for the abnormal post-contrast enhancement on CT scans in patients who are at risk to develop vasospasm. It may also be involved in the pathogenesis of vasospasm.

Denervation of cerebral perivascular nerves after subarachnoid hemorrhage has been demonstrated using electron microscopy and immunohistochemical techniques (36,45,68). Duff et al. (36) showed disintegration of both clear- and dense-core vesicles of perivascular nerves, fragmentation of varicosities, loss of Schwann cell cytoplasm, and axonal degeneration. The changes were most pronounced 7 days after the instillation of

blood in a cat model and correlated in time with maximal injury of the media and endothelium. Espinosa et al. (45) demonstrated loss of adventitial nerves on transmission electron microscopy in a primate model of subarachnoid hemorrhage. Hara et al. (68) showed a reduction of immuno-histochemical staining in acetyl-cholinesterase, vasoactive intestinal polypeptide, adrenergic, and substance P-like immuno-reactive perivascular nerves after subarachnoid hemorrhage as well as surgical manipulation of the vessel wall in a primate model of chronic vasospasm. The reduction in immunoreactive staining of perivascular nerves did not correlate with the development of angiographic vasospasm.

A discrepancy exists between the degree of proliferative vasculopathy in human autopsy material as opposed to experimental models. In general, the time period following subarachnoid hemorrhage and examination of human autopsy material is much longer than in the experimental models, allowing for a greater degree of proliferative change which is present long after angiographic spasm has resolved (17,32,45,85,114). Kapp et al. (80) propose that chronic vasospasm involves three phases: (1) the initial muscular contraction of

the arterial wall; (2) a secondary injury to the artery that consists of endothelial desquamation with adherence of platelets to the denuded internal elastic lamina; and (3) the repair process, which is the proliferative vasculopathy observed in human autopsy specimens.

ETIOLOGY

The transient nature of angiographic vasospasm suggests that the predominant mechanism of vessel lumen narrowing is prolonged smooth muscle cell contraction, despite the presence of morphological changes in the vessel wall. This is further supported by the fact that dramatic pathological changes in the vessel wall have been identified long after angiographic spasm has resolved (17,32,45,114). Peterson et al. (138) measured the in vitro basilar artery smooth muscle membrane potential by cell puncture with glass microelectrodes, in a canine model of chronic vasospasm. Vessels demonstrated to be in spasm by angiography were depolarized relative to control vessels not in spasm, further supporting the smooth muscle cell contraction theory of prolonged vasospasm.

PHYSIOLOGY OF VASCULAR SMOOTH MUSCLE CONTRACTION

Smooth muscle cells contract in response to pharmacological, neurotransmitter, electrical, and mechanical stimuli which result in either plasma membrane receptor stimulation or depolarization. This results in rythmic pulsed smooth muscle tone. Maintained tone is determined by a continous passive

leakage of extracellular Ca^{++} through the plasma membrane. All mechanisms that initiate smooth muscle contraction result in an increase of free cytosolic intracellular Ca^{++}. The degree of contraction is determined by the concentration of free intracellular Ca^{++}.

Adrenergic, serotonergic, cholinergic, histaminergic and prostaglandin receptors have been identified on vascular smooth muscle cell plasma membrane. Stimulation of these receptors may activate the enzymes guanyl cyclase or adenyl cyclase. Dephosphorylation of guanosine triphosphate or adenosine triphosphate to cyclic guanosine monophosphate (cGMP) or cyclic adenosine monophosphate (cAMP) follows activation of the membrane bound enzymes guanyl cyclase and adenyl cyclase, respectively. Cyclic-GMP acts as a second messenger to cause a release of protein bound Ca^{++} from the sarcoplasmic reticulum, elevate free intracellular Ca^{++} and effect muscle contraction. Cyclic-AMP has the opposite effect in decreasing free Ca^{++} and causing muscle relaxation. Alpha-adrenergic receptor stimulation results in vascular smooth muscle cell contraction by activation of the guanyl cyclase pathway. Beta-adrenergic receptor stimulation results in vasodilation

activation of the adenyl cyclase pathway. Receptor diated muscle contraction by the second messenger chanism is independent of extracellular Ca^{++} ncentration and will occur in calcium free solutions n assessed in vitro.

Receptor mediated muscle contraction may also rate by opening of receptor operated ion channels ch admit Ca^{++} (and/or Na) resulting in either influx extracellular Ca^{++} or membrane depolarization. This e of mechanism for receptor mediated muscle traction is dependent on extracellular Ca^{++} centration.

Smooth muscle contraction by membrane olarization or high potassium containing solutions olves activation of potential dependent channels ch result in movement of extracellular Ca^{++} into the l. Potential dependent muscle contraction and muscle traction produced by passive leakage of Ca++ across plasma membrane (maintained tone) is also dependent extracellular Ca++ concentration.

Free intracellular Ca^{++} initiates smooth muscle traction by binding to the protein calmodulin. This ulatory enzyme becomes activated and the Ca^{++}-modulin complex then binds and activates myosin light

chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of myosin light chain subunit. Actin-myosin interaction is stimulated by the phosphorylated myosin light chain and free intracellular Ca^{++} forms bridging cross-links between actin and myosin. The contractile tension of the smooth muscle cell increases with increasing free Ca^{++} concentration.

Muscle relaxation is produced by mechanisms which lower free intracellular Ca^{++}. Receptor mediated relaxation has been discussed above and involves the activation of membrane bound adenyl cyclase with resultant elevation of second messenger cAMP. Cyclic-AMP increases protein bound Ca^{++} within sarcoplasmic reticulum. A Ca-ATP-ase membrane pump exists which actively extrudes calcium from the cell into the extra-cellular space. This pump is probably stimulated when the smooth muscle cell membrane becomes repolarized.

Excellent reviews on the physiology of vascular smooth muscle cell contraction are provided by Bolton (21), Hartshorne and Mrwa (71), Flaim and Zelis (53), and Weiss (187).

VASOACTIVE CONSTITUENTS OF SUBARACHNOID BLOOD CLOT

Vasocontrictor activity has been identified in hemorrhagic CSF both clinically and experimentally (22,24,127,150). Erythrocytes, platelets, and products of the coagulation system all produce vasocontriction. In vitro studies on isolated canine basilar artery have noted significant contraction induced by fresh platelet rich plasma or serum which lose their contractile activity after 24 hours of incubation (126,131). Intact erythrocytes and platelet poor plasma have no contractile activity. However, lysed erythrocytes have contractile activity which reaches a plateau at three days of incubation and is maintained for at least 14 days (126). Biochemical analysis of the incubated erythrocytes by column chromotography revealed that contractile activity was present in only one peak of the chromatographically eluted fractions and was shown to possess a similiar absorption spectrum to that of hemoglobin. Other in vitro studies have shown vasocontrictor activity of hemoglobin (177,188,189). Tanishima (177) showed that the contractile activity of lysed erythrocytes was derived from oxyhemoglobin. Methemoglobin, a metabolic oxidative product of oxyhemoglobin had minimal vasocontrictor activity and

the constituents of hemoglobin caused little or no contraction compared to hemoglobin as a whole.

In vivo studies have also produced prolonged vasospasm from breakdown products of erythrocytes (128,166). Osaka (128) produced vasocontriction of cat basilar arteries by topical application of fresh serum and platelet rich plasma which was lost after incubation. However, severe prolonged spasm was produced by incubated fractions of lysed erythrocytes. Sonobe and Suzuki (166) observed the basilar artery contriction in cats with a surgical microscope. Topical application of fresh blood produced a weak and transient response. Supernatants of blood-CSF mixtures incubated for 3 days had weak activity in comparison with the powerful and long-lasting activity of those incubated for seven days. Mixtures incubated for 15 days had little or no activity. The vasospasmogenic substance in the 7th day mixture was identified as oxyhemoglobin. In the 15th day mixture, oxyhemoglobin was not identified, it was spontaneously converted to methemoglobin.

Fibrin-fibrinogen degradation products, plasmin, and thrombin have also been implicated in the etiology of vasospasm because of their in vitro vasocontrictor

properties (100,190,194). White et al. (190,194) have noted a marked contraction elicited by thrombin on isolated canine basilar arteries which was of short duration. Plasmin had a longer duration of vasoconstrictor activity and may be involved in delayed vasospasm in association with clot lysis.

The mechanism of action of oxyhemoglobin, platetets, and products of the coagulation cascade on contraction of vascular smooth muscle is unkown. Studies have focused on selective pharmacological antagonism of vascular smooth muscle receptors in the presence of various blood clot constituents. Most of the research has concentrated on alpha-adrenergic, serotonergic, and prostaglandin mediated vascular smooth muscle contraction. The discussion to follow is a review of the research involved in attempting to identify the vasoactive substance(s) in hemorrhagic CSF ultimately involved in sustained vascular smooth muscle cell contraction.

SEROTONIN

Serotonin is released from platelets following platelet aggregation. Allen et al. (11,12) studied in vitro contractile activity of serotonin on canine

basilar arteries and found a correlation of dose-response curves between serotonin and blood induced vasocontricion. They also found that most of the contractile activity of human CSF taken 2 to 7 days after subarachnoid hemorrhage was due to serotonin. Phenoxybenzamine irreversibly blocked the basilar arteries vasocontrictor response to serotonin, serum, and CSF. An in vivo study in dogs (10) demonstrated cerebral arterial spasm following an intra-cisternal injection of serotonin which lasted for at least 3 hours. Comparable spasm was produced by a blood injection containing approximately the same amount of serotonin. Phenoxybenzamine reversed both the spasm produced by serotonin and that produced by blood. Other investigators have not found inhibition of hemorrhagic CSF or oxyhemoglobin induced in vitro vasocontriction by the serotonin antagonist methysergide or by the alpha-adrenergic antagonists, phenoxybenzamine and phentolamine (126,127,150,177).

An increased sensitivity of cerebral vessels to serotonin and norepinephrine after experimental subarachnoid hemorrhage has been reported (98,170). These in vitro studies have shown the increased

sensitivity to be maximal at 3 days after subarachnoid hemorrhage and then gradually disappear. Young et al. (198) reported early onset serotonin hypersensitivity 6 hours after experimental subarachnoid hemorrhage, maximal at 36 hours and a gradual return to normal. They felt that the level of tension generated in the contracted basilar artery by serotonin was not of sufficient magnitude to implicate serotonin alone as the etiological agent for vasospasm.

Toda et al. (181) found a state of decreased sensitivity to serotonin, norepinephrine, histamine, and K^+ of canine middle cerebral arteries in prolonged spasm, 7 days after subarachnoid hemorrhage induction. Krueger et al. (91) also demonstrated reduced reactivity of monkey vessels in chronic vasospasm to serotonin, norepinephrine, and potassium chloride. Voldby et al. (183) measured the concentration of serotonin in ventricular CSF, between 2 and 15 days after aneurysmal subarachnoid hemorrhage. The levels measured did not differ from control patients and there was no correlation between CSF serotonin level, angiographic vasopasm, or clinical grade. However, cisternal CSF collected at the time of early surgery and contaminated by fresh blood did show a very high concentration of

serotonin in 2 patients with severe postoperative vasospasm.

The results do not support the theory that serotonin plays a major role in sustaining delayed vasospasm, but may be involved in the initiation of vasospasm, early after subarachnoid hemorrhage and following platelet aggregation.

NOREPINEPHRINE

Subarachnoid hemorrhage produces a denervation of cerebral perivascular nerves with a marked loss of catecholamine immunoreactive staining and reduced norepinephrine content (36,40,58,68,97). Fraser et al. (58) postulated an exhaustion of norepinephrine stores in perivascular nerve terminals following repeated spasm of the vessels. They considered that blood contains a vasocontrictor substance which stimulates the alpha-adrenergic receptor to produce cerebral vasospasm. Conficting reports of denervation hypersensitivity of cerebral vessels to norepineprine and serotonin have been mentioned above (91,98,170,181,200). Conflicting reports of inhibition of hemorrhagic CSF or oxy-hemoglobin induced vasoconstriction by alpha-adrenergic antagonists, have also been mentioned above (10,12,150, 177).

Alksne and Greenhoot (5) produced myonecrosis of the media in the basilar artery of a primate model of delayed vasospasm by injection of norepinephrine into the prepontine cistern. An intense immediate vasospasm was produced which lasted only minutes and was followed by a second stage of spasm that persisted for 8 to 10 days. Degenerative morphological changes of the blood vessel wall similar to that seen after subarachnoid hemorrhage were also found.

Shigeno (161) measured postoperative norepinephrine levels in ventricular and cisternal samples in patients operated on for aneurysmal subarachnoid hemorrhage. Cisternal CSF of patients with vasospasm contained significantly higher norepinephrine levels compared to those without vasospasm. However, the increase was not considered high enough to locally constrict cerebral arteries. The possibility of a secondary phenomenon of norepinephrine release into the CSF from various sources in the brain was considered.

PROSTAGLANDINS

Prostaglandins are ubiquitous substances with biosynthetic components common to an enormous spectrum of cells (79). Synthesis involves the conversion of

phospholipids to the precursor fatty acid arachidonic acid, by the enzyme phospholipase A. Arachidonic acid is converted to biologically active eicosanoids by the enzymes lipoxygenase and cycloxygenase. Lipoxygenase conversion gives rise to the leukotrienes which modulate the immune response. Cycloxygenase conversion gives rise to the endoperoxides (PGG_2 and PGH_2) which are subsequently converted to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin), and thromboxane A_2. The endoperoxide derivative prostaglandins have potent effects on smooth muscle contraction and platelet aggregation (79).

Prostaglandins are synthesized in cerebral blood vessels. Hagen et al. (65) studied cerebral artery prostaglandin synthesis using thin layer chromotography following incubation of vessels with (1-^{14}C)-arachidonic acid. Five products of arachidonic acid were identified: PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin, and thromboxane B_2 (stable metabolite of thromboxane A_2). Maeda et al. (103) and Saski et al. (154) found similiar results, however prostacyclin was the most abundant prostaglandin found in cerebral vessels. Prostacyclin is mainly generated in the endothelium (104). Following experimental subarachnoid hemorrhage, prostacyclin synthesis is substantially diminished between days 3 and

8 after subarachnoid hemorrhage induction (103,104,154). Measurement of 6-keto-prostaglandin $F_{1\alpha}$, a stable metabolite of prostacylin, in CSF of patients with ruptured aneurysms has also shown reduced levels (144).

The eicosanoids thromboxane A_2, $PGF_{2\alpha}$, PGE_2, PGE_1, and PGA_1 have all shown in vitro vaso-contrictor properties (39,67,75,199). In vivo vaso-contriction of cerebral vessels has also been demonstrated using intra-arterial PGE_1 and $PGF_{2\alpha}$ infusions (192,197). However, radioimmunoassay of $PGF_{2\alpha}$ in CSF from patients with subarachnoid hemorrhage showed no correlation between the levels and the appearance of vasospasm (93). Prostacyclin has produced in vitro relaxation of vascular smooth muscle as well as inhibition of contractions induced by thromboxane A_2, $PGF_{2\alpha}$, serotonin, noradrenaline, and angiotensin II (23,29,75,134).

The effects of thromboxane A_2 and prostacyclin appear to directly oppose one another. Thromboxane A_2 inhibits adenyl cyclase by plasma membrane receptor stimulation and thereby lowers cAMP, and increases free intracellular Ca++ with subsequent smooth muscle contraction. Prostacyclin has the reverse effect, in that it stimulates adenyl cyclase. Thromboxane A_2 is

synthesized by platelets and serves to counteract the effects of injury by causing vasoconstriction and inducing platelet aggregation. Prostacyclin is synthesized by endothelial cells and produces vasodilation and inhibition of platelet aggregation. The balance between thromboxane A_2 and prostacyclin may be responsible for the moment to moment control of blood flow (79). Endothelial cell injury, commonly seen in cerebral vasospasm results in decreased prostacyclin production. Enhanced platelet aggregation in response to endothelial injury results in increased thromboxane A_2 release. The disordered physiological control of the calibre of the cerebral arteries may be responsible for sustained vasospasm (23,157). This mechanism relates degenerative morphological vessel changes with enhanced pathophysiological smooth muscle contraction, producing chronic cerebral vasospasm.

LIPID HYDROPEROXIDES

Oxyhemoglobin's potent vasocontricting effect has been mentioned above. In addition, oxyhemoglobin can initiate free radical reactions following conversion to methemoglobin (14,155). Activated species of oxygen such as superoxide anion, hydrogen peroxide, and singlet

oxygen are released. These activated oxygens initiate free radical reactions with unsaturated fatty acids found in cell membranes producing various lipid peroxides (partial oxidation products possessing single unpaired electrons). Membrane disruption follows (129). Endogenous peroxidation inhibitors such as the intracellular enzymes catalase and superoxide dismutase normally prevent the accumulation of free radicals. However, a change in the ratio of free radicals to inhibitors may lead to pathological changes.

Sasaki et al. (157) studied the effect of the lipid hydroperoxide, 15-hydroperoxy arachidonic acid: 15-HPAA, on in vivo production of chronic vasospasm in a canine model. The 15-HPAA was injected into the cisterna magna and produced a biphasic constriction of the basilar artery. The initial contriction phase lasted for 10 hours and was followed by a second phase, beginning 48 to 72 hours after the injection. The secondary constriction persisted until sacrifice. The prolonged arterial constriction was associated with electron microscopic changes of severe endothelial degeneration and mild myonecrotic changes in the tunica media.

Peroxidation of phospholipids in endothelial cell membranes following subarachnoid clot lysis may account

for the endothelial cell degeneration. Disruption of the normal physiological balance between thromboxane A_2 and prostacyclin would then account for the sustained smooth muscle contraction of chronic vasospasm. The vasoconstrictor substances previously mentioned such as oxyhemoglobin, serotonin, norepinephrine, thrombin, and plasmin may all contribute in a multifactorial etiology.

TREATMENT

Therapy for chronic vasospasm after subarachnoid morrhage has involved: early aneurysm surgery and moval of subarachnoid clot; pharmacological dilation vasospastic cerebral vessels; treatment of cerebral chemia with hypervolemic/hypertensive therapy; and rebral protection from infarction by barbiturates.

RLY SURGERY AND CLOT REMOVAL

When intracranial surgery for ruptured aneurysm rst became popular in the 1950's, prevention of tastrophic rebleeding by aneurysm clipping was the imary concern and operations were performed on an gent basis. However, an unacceptable operative rtality occurred. Surgeons encountered a swollen, morrhagic, soft brain which required excessive traction. Visualization of vital structures was fficult and the friable aneurysm frequently ruptured traoperatively before successful obliteration. Graf) reported an 80 % operative mortality in 1955 from s type of surgery.

Attention then turned to improving operative rtality by delaying surgery, and allowing patients to

recover from the acute effects of subarachnoid hemorrhage. Improved operative conditions reduced operative mortality. Norlen and Olivecrona (118) reported a 3 % operative mortality in patients who were operated on in good condition, at least 21 days after the subarachnoid hemorrhage. The policy of delayed operation continued for about the next 20 years.

Delayed operation did not improve the overall management mortality because many patients died of recurrent hemorrhage or vasospasm while waiting for surgery. Weir and Aronyk (185) reported an increased management mortality in poor grade patients who were operated on between 10 and 32 days after subarachnoid hemorrhage, compared to poor grade patients who were operated on within 3 days of hemorrhage. Kassell et al. (82) reported an 81 % favorable outcome, 7 % unfavorable outcome, and 11 % mortality in patients who were operated on within 3 days of subarachnoid bleeding. The overall management results for patients in whom surgery was planned at least 7 days after the last hemorrhage showed a 42 % favorable outcome, 17 % unfavorable outcome, and a 42 % mortality. The rebleeding rate for the late group was 29 %, compared to 0 % in the early group. The number of medical

complications, length of hospitalization, and development of symptomatic vasospasm were all greater in the late group. Vasospasm in the early group occurred only postoperatively, and with the aneurysm obliterated was treated more aggressively and successfully with hypertensive/hypervolemic therapy. The predominately preoperative vasospasm in the late group could not be treated aggressively in this way because of the unsecured aneurysm.

Improved microneurosurgical instrumentation and neuroanesthesia have provided the present day neurosurgeon with a slack brain and accurate visualization. This has resulted in a much improved operative morbidity and mortality for early aneurysm surgery (83).

Prevention of vasospasm by early aneurysm surgery and aggressive removal of subarachnoid blood has been reported by Mizukami et al. (113). Sixty-four patients underwent surgery within 4 days of subarachnoid hemorrhage. The subarachnoid clot was removed by microsurgical suction-irrigation after clipping of the aneurysm. Postoperative CT scans showed that it was possible to remove the majority of the blood clot except for that located in the frontal interhemispheric

fissure, the posterior insular cistern on the approached side, and all the insular cistern on the contralateral side. There was no angiographic vasospasm or only mild spasm in any site where the blood clot had been successfully removed. Delayed neurological deficits occurred only in those cases in which subarachnoid blood clot remained in the cisterns. Taneda (175) reported a reduction in the incidence of permanent delayed neurological deficit from 27.7 % to 10.9 % using early surgery (within 48 hrs.) with extensive, aggressive clot removal. Ljunggren et al. (95) reported a 20.9 % incidence of delayed ischemic deficits with a 10 % mortality in patients who underwent early operation with removal of subarachnoid clots and rinsing of the basal cisterns.

Although, the incidence of vasospasm and delayed ischemic deficits appears to be less in patients who have had aggressive early subarachnoid clot evacuation, this risk has not been eliminated because complete clot evacuation is frequently impossible. Excessive efforts at clot evacuation in the acute stage may worsen brain swelling and induce the formation of intracerebral hematomas (35,130). The risk of fatal postoperative vasospasm may be greater in patients who

have surgery between the 4th and 7th day after subarachnoid hemorrhage (35,149,169,172). Therefore, early surgery for aneurysm clipping and reduction of vasospasm should be performed within the first 3 days after subarachnoid hemorrhage (149).

In an experimental primate model of chronic vasospasm, Nosko et al. (124) showed prevention of angiographic vasospasm and delayed ischemic deficits by complete subarachnoid clot removal 24 hours after SAH induction. Handa et al. (66) studied the effect of timing of clot removal on chronic vasospasm in the same primate model. Evacuation of subarachnoid clot later than 48 hours after SAH induction resulted in no significant reduction in the degree of chronic vasospasm. The authors suggest that clot removal at early operation is likely to be useful only if it is performed within 48 hours of SAH.

Since complete clot evacuation by mechanical means is extremely difficult and may be dangerous in the clinical situation, adjunctive attempts at clot removal with CSF lavage and intrathecal fibrinolytic agents have been tried both clinically and experimentally (2,4,132,133,149,198). Alexander et al. (2) reported no benefit of cisternal lavage with 120 ml of artificial

CSF, in the two-hemorrhage canine model of chronic cerebral vasospasm, in spite of evidence for significant reduction of gross clot by lavage. Lysis of subarachnoid clot and a more rapid disappearance of perimesensephalic high densities on CT scan (within 7 days) has been reported using intrathecal urokinase in humans (198). Pang et al. (132,133) produced complete lysis of solid intraventricular clots in 3 to 6 days in a canine model, by using 20,000 IU of intraventricular urokinase every 12 hours. They found no complications of hemorrhage, or inflammatory changes in the brain or meninges. Alksne et al. (4) reported a significant reduction of pathological changes of chronic cerebral vasospasm in a two-hemorrhage pig model, using an intracisternal injection of 100 units of the thrombolytic agent, plasmin. The effectiveness of plasmin or urokinase in preventing arterial narrowing after subarachnoid hemorrhage has not yet been reported.

CEREBRAL VASODILATION

I. Calcium Antagonists - Calcium Entry Blockers

Calcium antagonist compounds are potent smooth muscle cell relaxants and act by inhibiting the accumulation of free intracellular Ca++. They may be

classified into two types 1) calcium entry blockers, which act by inhibiting the influx of extracellular Ca++ into cells; and 2) intracellular antagonists which inhibit the action of intracellular Ca++ by binding to calmodulin (173). Examples of the former compounds are: nifedipine, nimodipine, nicardipine, diltiazem, verapamil, and D600. The latter compounds include antipsychotics such as trifluoperazine and HA compounds which are sulfonamide derivatives prepared by modification of a calmodulin antagonist. The calcium entry blockers are widely used in coronary artery disease and supraventricular arrythmias. They have recieved the most attention in the study of therapy for cerebral vasospasm.

In vitro studies have demonstrated a potent inhibitory action of calcium entry blockers on isolated cerebral artery contractions induced by various agonists such as serotonin, prostaglandin $F_{2\alpha}$, thrombin, norepinephrine, whole blood, and K^+ (9,46). Others have found a greater selectivity of inhibition to various agonist induced contractions. Takagi et al. (171) reported a greater degree of inhibition to K^+ induced contractions than serotonin or norepinephrine. Nosko et al. (121) showed that K^+ induced contractions

of isolated cerebral arteries were effectively blocked at low concentrations of nimodipine (10^{-9} M), whereas norepinephrine and serotonin induced contractions were more resistant to blockade. Hemoglobin and prostaglandin $F_{2\alpha}$ were antagonized poorly even by high concentrations of nimodipine (10^{-7}M). Potassium induced smooth muscle contraction has a greater dependence on influx of extracellular Ca^{++} through potential dependent channels. Calcium entry blockers may therefore be more effective on inhibition of K^{+} induced contraction which does not activate membrane receptors and mobilize intracellular stores of Ca^{++} through the second messenger mechanism.

In vitro selectivity of calcium entry blockers for cerebral vessels compared to systemic vessels has been demonstrated (8,25,). Calcium entry blockers inhibit serotonin, phenylephrine, PGF_{2alpha}, norepinephrine, and K^{+} induced contractions more effectively in cerebral vessels than in systemic vessels. It is possible that cerebral vessels are more dependent on extracellular Ca^{++} influx following membrane receptor stimulation. Activation of receptor operated channels may be more important in cerebral vessel contraction as opposed to second messenger pathways and mobilization of

intracellular Ca++ stores.

The relative order of potency for calcium entry blockers on isolated cat pial arteries was: nimodipine > nifedipine > D600 > verapamil > diltiazem (184).

Species variation in susceptibility to nimodipine has been shown using in vitro studies (121). Isolated cerebral arteries from dog, monkey, and human specimens showed similiar sensitivity to nimodipine inhibition of K^+, hemoglobin, and prostaglandin $F_2\alpha$ induced contractions. However, in the case of vessels with contractions induced by serotonin and norepinephrine, monkey arteries were significantly less sensitive to nimodipine than human or dog vessels. Species variation of pharmacological sensitivity must be considered when evaluating therapy in different in vivo animal models.

In vivo experimental studies have confirmed the relative cerebral vascular selectivity of calcium entry blockers. Using the ^{133}xenon clearance technique, McCalden et al. (109) found an 18 % increase in cerebral blood flow in baboons after intravenous nimodipine infusion (1 mcg/kg/min). There was no alteration in systemic blood pressure or cerebral oxidative metabolism. However, at infusions above 10

mcg/kg/min arterial pressure decreased with a return of cerebral blood flow to baseline. Harper et al. (70) reported that an intravenous infusion of 2 mcg/kg/min of nimodipine in primates produced a modest fall in mean arterial blood pressure and a 27 % increase in cerebral blood flow which lasted 50 minutes after the infusion was stopped. Intra-arterial infusion of 0.67 mcg/kg/min, increased cerebral blood flow 46 to 57 % and this was increased to 87 % after disruption of the blood-brain barrier with hyperosmolar urea. Nosko et al. (122) showed significant hemodynamic abnormalities of nimodipine when given in large oral doses. Nimodipine 6- and 12-mg/kg produced a 23 % and 33 % decrease in mean arterial pressure, respectively. Thus, even though nimodipine has been reported to have selective action on cerebrovascular smooth muscle, the preferential action is relative and dose dependent.

Allen and Bahr (8) reported beneficial effects of sublingual nifedipine in reversing and preventing acute and chronic vasospasm in a single hemorrhage canine model. Varsos et al. (182), Gioia et al. (60), and Zabramski et al. (202) reported no benefit of sublingual, oral, or intravenous nifedipine or nimodipine in preventing or reversing chronic vasospasm

in the two-hemorrhage and multi-hemorrhage canine models. In the primate model of chronic vasospasm, Espinosa et al. (43) and Nosko et al. (123) found that oral nimodipine in doses of 1, 3, 6, and 12 mg/kg every 8 hours did not reduce the incidence of vasospasm nor the degree of vessel narrowing on angiography, compared to placebo. Delayed ischemic deficits were seen in 33 % of animals recieving the 12 mg/kg dose, compared to 0 % in the other nimodipine groups and 5 % in the placebo group.

Although systemic administration of calcium entry blockers has not been effective in experimental models of chronic vasospasm, Gioia et al. (60) found that intrathecal nimodipine (4 ml-10^{-3} M) promptly and completely reversed angiographic vasospasm in all animals in the two-hemorrhage canine model. The effect lasted at least 4 hours and had disappeared by 24 hours. An intrathecal dose of 4 ml of 10^{-4} M was without effect. Sublingual (0.28-0.58 mg/kg) and intravenous (0.1 mg/kg) nimodipine produced persistent hypotension without affecting vasospasm. In a preliminary trial of intracisternal nimodipine or nifedipine (100 mcg) in a multi-hemorrhage canine model, Zabramski et al. (202) also found a more beneficial effect of intrathecal

compared to systemic administration. However, only partial resolution of chronic vasospasm occurred in 4 of 6 animals when evaluated by repeat angiography, 20 to 30 minutes after subarachnoid administration. It has been suggested that intrathecal nimodipine or nifedipine may be effective for the emergency treatment of vasospasm in humans (60,202). The high lipid solubility of nimodipine may allow for a long duration of action when given intrathecally. Water-soluble compounds such as diltiazem are easily removed by washout in vitro and would have a much shorter duration of action. Nimodipine or nifedipine must be dissolved in organic solvents containing polyethylene glycol 400 and absolute ethanol. The effect of repeated intrathecal administration of these compounds has not been evaluated.

Nimodipine has been administered orally, intravenously, and intrathecally in various clinical trials (7,15,16,63,96,158). In a multi-centre, prospective, double-blind, placebo-controlled trial of 125 neurologically normal patients after aneurysmal subarachnoid hemorrhage, Allen et al. (7) reported a reduced incidence of severe delayed ischemic deficits causing permanent deficit or death in patients treated

with oral nimodipine compared to placebo (1.8 % of patients given nimodipine, 13.3 % of patients given placebo). However, the effect on prevention of angiographic spasm was not assessed and the incidence of total delayed ischemic deficits (transient/permanent) was not statistically different between nimodipine and placebo groups. Ljunggren et al. (96,158) and Auer (15,16) used intraoperative topical nimodipine (2.4×10^{-5} M) over exposed vessels after aneurysm clipping, followed by postoperative intravenous nimodipine (0.25-0.5 mcg/kg/min, 7-14 days), followed by oral nimodipine (240 mg/day until day 21 after subarachnoid hemorrhage). Delayed ischemic cerebral deterioration with permanent neurological dysfunction occurred in 1.7-5.9 % of patients. The appearance and severity of late angiographic vasospasm was not affected by nimodipine. Grotenhuis et al.(63) found no change in cerebral vessel caliber on angiograms after an intracarotid slow bolus injection of nimodipine in 6 patients with vasospasm after subarachnoid hemorrhage. Auer (16) reported that a 1 mcg/kg/min intravenous nimodipine infusion in patients during EC-IC bypass surgery, produced a 16 % dilation of pial arteries (dilation of small arteries was more marked than that of

larger vessels). Perivascular application of nimodipine during aneurysm surgery evoked a 70-80 % dilation of pial arteries (16). Postoperative intracisternal nimodipine (0.2 mg/1 ml) administered via a cisternal catheter produced angiographic dilation in 9 of 12 patients. However, only 4 patients had angiographic vasospasm (all were asymptomatic) and not all vessels dilated. Fibrosis in the subarachnoid space may have prevented even distribution of the drug.

Systemic administration of nimodipine has not proven effective in prevention or reversal of angiographic vasospasm in experimental or clinical trials. Clinical trials have shown a protective effect in reducing the severity of cerebral ischemia from vasospasm in predominately good grade patients (7,15,16,96,158). A present multi-centre, double-blind placebo-controlled trial of oral nimodipine in poor grade patients is being conducted. Systemic nimodipine may be exerting it's protective effect by opening pial collateral vessels. It's effect on large inflow vessels seen angiographically is less than the effect on small vessels which may not be visualized angiographically (16). Meyer et al. (111) noted a statistically significant improvement in cortical blood

w, intracellular brain pH, and EEG attenuations in bits given intravenous nimodipine infusions prior to following middle cerebral artery occlusion, compared controls. There was reversal of cortical pallor and ll vessel spasm following nimodipine treatment. Also, rotective effect of nimodipine on neuronal metabolism occur after cerebral ischemia by inhibition of ntial dependent Ca^{++} channels and prevention of an ntrolled calcium flux into neurons. This Ca^{++} flux cipitates a cascade of biochemical events involving staglandins and free radicals, leading to versible neuronal damage after ischemia (111).

Intracellular Calcium Antagonists

Calmodulin antagonists such as the antipsychotics rpromazine and trifluoperazine have been stigated in the two-hemorrhage canine model ,137). Reversal of delayed angiographic vasospasm partial and inconsistent in the small groups of als studied.

Takayasu et al. (173) have studied a new intra- ular Ca^{++} antagonist, HA compounds HA1004 and 07; sulfonamide derivatives prepared by modification the calmodulin antagonist W-7. These compounds

produced a mild dilation of the basilar artery in the two-hemorrhage canine model when administered intravenously. The degree of dilation ranged from 10 % to 27 % above vasospastic control vessels. Intracisternal administration of 6 mg completely reversed chronic vasospasm with a 44 % dilation above vasospastic controls. The intracisternal effect lasted at least 4 hours.

III. Phosphodiesterase inhibitors/Adrenergic agents

Pharmacological agents which inhibit the enzyme phosphodiesterase result in an increase of intracellular cAMP which acts as a second messenger to decrease free intracellular Ca^{++} and effect smooth muscle cell relaxation. The phosphodiesterase inhibitors: phthalazinol, and aminophylline have produced inconsistent beneficial results in clinical and experimental vasospasm (54,55,94,182). Results in the superior experimental models such as the two-hemorrhage canine model have not shown any benefit of these compounds (182). Beta-adrenergic agonists (increase cAMP) and alpha-adrenergic antagonists (decrease cGMP) have also shown variable results on reversal of vasospasm (10,72,164,167).

IV. Antiserotonin Compounds

Reserpine and Kanamycin deplete platelet-borne serotonin and reduce the uptake of and storage of vasoactive amines. Zervas et al. (203) reported the beneficial preventive effects of these compounds in a primate model when blood serotonin levels were reduced to more than 75 %. However, Noseworthy et al. (119) found no evidence that these compounds prevented vasospasm in a similiar primate model. Blumenkopf et al. (20) did not prevent the development of angiographic vasospasm by administration of reserpine and kanamycin in patients with subarachnoid hemorrhage, despite lowering serum serotonin and norepinephrine levels.

V. Anti-inflammatory/prostaglandin agents

Steroidal and non-steroidal anti-inflammatory agents all interfere with prostaglandin synthesis which may produce vasocontriction, vasodilation, or reduce inflammation depending on the selectivity of various agents on different prostaglandin compounds.

Chyatte et al. (30,31) reported prevention or reduction of angiographic vasospasm and degenerative smooth muscle abnormalities in the two-hemorrhage dog

model by using ibuprofen or high dose methly-prednisolone. These authors believe that chronic cerebral vasospasm is a structural derangement of the blood vessel wall caused by an inflammatory response producing a proliferative vasculopathy and vessel narrowing.

White and Robertson (193) found a significant reduction in the occurrence of acute vasospasm in a single hemorrhage dog model by using various non-steroidal anti-inflammatory agents, suggesting a vasodilator mechanism. Prostacyclin infusion via the vertebral artery failed to reverse the vasospasm present 24 hours after subarachnoid hemorrhage induction. Fukumori et al. (59) failed to reverse delayed angiographic vasospasm in dogs by intravenous infusion of prostacyclin and indomethacin. These agents also did not increase cerebral blood flow. Systemic blood pressure was significantly reduced by prostacyclin infusion.

Sasaki et al. (156) found the selective thromboxane synthetase inhibitor, OKY-1581 to almost completely abolish the appearance of late angiographic vasospasm in dogs. Degenerative changes in the endothelium and media were present in the treated dogs, however

corrugation of the internal elastic lamina was absent compared to controls. In a clinical trial of OKY-1581 intravenous infusion, a suggestive but statistically insignificant improvement was found in angiographic vasospasm, ischemic symptoms, and overall outcome (176).

TREATMENT OF CEREBRAL ISCHEMIA

Observations of reduced red cell mass, and total blood volume in subarachnoid hemorrhage patients, as well as increased delayed ischemic deficits in these patients receiving diuretics, supports the use of intravascular volume expansion with red blood cells and colloid in the prevention and treatment of ischemic complications from cerebral vasospasm (92,105,146).

Finn et al. (51) repeatedly reversed pre- and post-operative neurological deficits in patients with aneurysmal subarachnoid hemorrhage by increasing the pulmonary wedge pressure. In several patients an optimal wedge pressure was determined, below which deficits would reappear. This optimal wedge pressure most frequently ranged from 14 to 16 mmHg.

Kassell et al. (87) reported on the treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension in

58 patients with ischemic deficits. The most effective regimen consisted of volume expansion with blood and colloid solutions, blockade of the vagal depressor response with atropine, blunting of the diuresis with vasopressin, and elevation of arterial blood pressure with vasopressors such as dopamine. The blood pressure was raised to whatever level was required to sustain acceptable neurological function with maximal limits of 240 mmHg systolic and 150 mmHg mean in patients whose aneurysms had been clipped. In patients with untreated aneurysms, 160 mmHg was the maximum limit of induced hypertension. A 20- to 100-mmHg increase in systolic arterial pressure was maintained for 12 hours to 8 days. Neurological deterioration was reversed in 81 % of patients and permanent improvement occurred in 74 % of patients. Complications included pulmonary edema, hyponatremia, aneurysmal rebleeding, coagulopathy, hemothorax, and myocardial infarction. They concluded that intravascular volume expansion and induced hypertension is effective in reversing ischemic deficits from vasospasm provided that treatment commences before cerebral infarction, adequate pressures are maintained for a sufficient period (longer than 1 week if necessary), meticulous attention is paid to hemodynamic,

biochemical, and hematological parameters, and the aneurysm has been successfully obliterated.

PROTECTION FROM CEREBRAL INFARCTION

The protective effect of barbiturates in focal cerebral ischemia has been documented (160). Selman and Spetzler stress the value of intraoperative barbiturate therapy for patients in whom temporary vessel occlusion will be required. The barbiturate therapy must be started within 1/2 hour after vessel occlusion and recirculation of blood flow must occur within 6 hours (160). The mechanism of CNS protection is not precisely known, but may involve reduction in cerebral metabolic rate, an increase in blood flow to ischemic regions, scavenge free radicals, and/or prevent edema.

The protective effect of barbiturates on cerebral ischemia from vasospasm after subarachnoid hemorrhage has not been demonstrated. Kassell et al. (86) reported the use of barbiturates in 12 patients with life-threatening neurological deficits from vasospasm refractory to other measures. Eleven of the 12 patients died despite aggressive therapy with hypertension and hypervolemia, ICP monitoring and therapy with CSF drainage, hyperventilation, mannitol, steroids, and

barbiturates. The discouraging results were most likely a reflection of the severity of the patients' condition prior to initiation of barbiturate therapy.

Anticipation of cerebral ischemia prior to it's occurrance is possible in very few clinical situations. Intraoperative circumstances of cerebral ischemia are the easiest to anticipate and implement protective barbiturate therapy, as mentioned above. Since there is a significant delay in the development of cerebral infarction following ischemic deficits produced by vasospasm, this clinical situation may also be one where barbiturate therapy may be beneficial if started early.

Ohta et al. (125) reported the results of a clinical trial using a new medication, nizofenone on subarachnoid hemorrhage patients. Nizofenone has been shown experimentally to have a greater effect than pentobarbital in reducing infarction size in cats with middle cerbral artery occlusion (174). This medication is an imidazole (thromboxane sythetase inhibitor) derivative and is thought to be a free radical scavenger. This clinical study showed no significant decrease in mortality, compared to the placebo control group. However, a higher percentage of survivors in the nizofenone group exhibited a good outcome (82 % vs.

68 %). No significant side effects were observed. This medication appears to be safer than barbiturates and was considered by the authors to be of clinical value in patients who are likely to suffer poor functional recovery from delayed ischemic deficits, despite it's negligible effect on survival rate.

SUMMARY

The preceding review shows clearly how extensive the research has been into the etiology, pathogenesis, and treatment of cerebral vasospasm, over the past 20 to 30 years. Numerous investigators have claimed success in either discovering the cause or cure for vasospasm, only to have these discoveries discredited by other investigators. A complete understanding of the etiology and pathogenesis of chronic cerebral vasospasm is not yet available, nor is there an unequivocally effective therapeutic modality. However, significant advances have been made over the past 20 to 30 years.

As investigators, we must maintain a critical review of the literature, especially in this day of individual promotion through quantity of publication. Reports of clinical trials which are not randomized and blinded, must be viewed with skepticism. Reports of experimental studies using inferior animal models of chronic vasospasm, must also be viewed with skepticism. As investigators, we can only hope to find specific areas of deficiency with potential for a beneficial contribution of knowledge to this field.

One such specific area concerns the use of intrathecally applied calcium antagonists. Results have been reported in clinical and experimental trials which suggest an effective therapeutic modality. However, clinical trials were not prospective and controlled; experimental trials used inferior animal models; and the safety of these agents when repeatedly applied intrathecally has not been verified in an animal model, before clinical use.

The study described in this thesis evaluates the effect of repeated intrathecal administration of nimodipine on the safety, prevention, and treatment of chronic vasospasm in a reliable, reproducible primate model.

CHAPTER TWO: THE PRESENT STUDY

OBJECTIVES

The present study described in this thesis was performed in order to evaluate the efficacy of intrathecal nimodipine therapy in a primate model of chronic vasospasm after subarachnoid hemorrhage. The specific objectives included: 1. prevention of angiographic vasospasm and pathological chronic vasospasm; 2. prevention of delayed ischemic neurological deficits; 3. reversal of established angiographic chronic vasospasm; and 4. safety of repeated intrathecal administration of nimodipine.

The animal care and surgical procedures were performed to achieve the standards of the Canadian Council on Animal Care. This study was approved by the Animal Ethics Committee of the University of Alberta.

MATERIALS AND METHODS

RANDOMIZATION

Twenty-four female cynomolgous monkeys (Macaca fascicularis) weighing an average of 3.4 kg (range 2.6 to 4.0 kg) were divided by restricted randomization into 3 groups of 8; sham (operative control), clot placement (non-treatment control), and clot placement plus intrathecal nimodipine therapy (treatment group).

BASELINE ANGIOGRAPHY

All animals underwent baseline cerebral angiography under general endotracheal anesthesia with controlled ventilation using a variable phase animal respirator (Harvard Apparatus, Inc., Millis, Massachusetts). Anesthesia was induced by using ketamine hydrochloride (6-10 mg/kg, i.m.). Anesthesia was maintained by using $N_2O:O_2$ (2:1 mixture) and gallamine paralysis (2 mg/kg q45min). The $PaCO_2$ was maintained near 40 mmHg by adjusting the tidal volume. Body temperature was maintained at 37°C by a heating pad placed beneath the animal and monitored by a rectal thermometer and thermostat (Tele-thermometer; Yellow Springs Instrument Corp., Yellow Springs, Ohio).

Procaine penicillin (100,000 IU/kg) was administered intramuscularly before any surgical procedure. The operative areas were shaved and prepared with Betadine surgical scrub solution.

The femoral artery was surgically exposed by a cutdown procedure under magnification. Topical lidocaine (2%) was placed on the artery to prevent constriction. The femoral artery was then catheterized by a 5-French, radiopague, polyethylene catheter through an arteriotomy between silk ligatures. Under fluoroscopic control the catheter was advanced into the innominate artery and it's position confirmed by a 1 ml injection of iothalamate meglumine 60% contrast medium.

The catheter was used for arterial blood pressure and heart rate monitoring, obtaining arterial blood gas samples, and for angiography. Patency of the catheter was maintained by intermittent flushing using heparinized saline (heparin 10 IU/100 ml 0.9% saline). The catheter was connected to a 3-way stopcock and pressure transducer for arterial blood pressure monitoring (Statham P23dB pressure transducer; Statham Instrument Co., Oxnard, California) and recorded using a Beckman Dynograph R611 eight channel recorder.

One arterial phase, anteroposterior angiographic

was obtained by injecting 10 ml of iothalamate mine at 300 psi. via a Cordis Injector (Cordis , Miami, Florida). The X-ray beam was centered at nimal's nasion and directed parallel to the orbito- l line. Radiographic exposures of 75 KeV at 2.5 nd 1/160 second were used. Magnification was kept ant between angiograms by maintaining a table to distance of 80 cm and a nasion to film distance of . A radiopaque control standard was used for er correction to constant magnification. action angiographic films were made on all animals sed for angiographic vessel caliber measurement.

After the angiogram, the catheter was removed and emoral artery ligated. The groin incision was ated with bacitracin solution and the wound closed interrupted 3-0 monofilament polyethylene sutures alon; Davis & Geck, New York, New York). After the dure, paralysis was reversed with prostigmine (0.07 i.v.) and atropine (0.02 mg/kg i.v.). The animals extubated following return of the gag reflex.

NDUCTION

The subarachnoid hemorrhage induction procedure was rmed 3 days after baseline angiography. All

animals underwent general endotracheal anesthesia with controlled ventilation and intra-arterial monitoring as performed for baseline angiography, with the addition of sodium pentobarbital (26 mg/kg i.v.). The $PaCO_2$ was maintained at 30 mmHg. The animal's head was placed in a 3-point fixation vise.

Using sterile surgical technique, a right fronto-temporal semi-circular scalp flap was reflected anteriorly using a cutting cautery. The temporalis muscle was incised with cutting cautery and reflected posteriorly. A 1.5 cm craniectomy was then performed using a trephine and Cloward ronguer. Bleeding from scalp and muscle was controlled with cautery and bleeding from bone was controlled with bone wax. The sphenoid ridge was ronguered to the base of the skull in order to faciliate brain retraction. The dura was opened in a semi-circular manner and reflected anteriorly. Bridging veins from the Sylvian fissure to the dura were coagulated with bipolar cautery and divided. The temporal lobe was retracted posteriorly using a tapered 1 mm self-retaining Sugita retractor. Cottonoids were placed over the brain and under the retractor in order to protect the brain from retractor contusions (fig 1A). A slack brain was achieved by

barbituate anesthesia, hyperventilation, and drainage of cerebrospinal fluid (CSF) from the basal cisterns. Arachnoid dissection of the basal cisterns was performed using microsurgical technique with sharp and blunt dissection of the arachnoid membrane to expose the intracranial blood vessels. The supraclinoid internal carotid artery was identified between the optic chiasm and oculomotor nerve (fig 1C). The arachnoid was dissected to expose the internal carotid, anterior cerebral, and middle cerebral arteries (fig 1B). The posterior communicating artery was followed from it's origin at the internal carotid artery to it's termination at the proximal posterior cerebral artery. Liliequist's membrane was opened, exposing the proximal posterior cerebral artery and the posterior intracranial circulation (fig 1D). Autologous blood clot taken from the femoral artery (4 ml) was then carefully placed around the exposed vessels in the clot group animals (fig 2A,B). The sham group animals had normal saline instilled in the dissected subarachnoid space in place of blood clot. An Ommaya reservoir was placed on the right side with the silicone catheter placed in the basal cisterns (fig 3A), brought out through the dura (fig 3B), and connected to the reservoir which was

Figure 1

Arachnoid dissection of the basal cisterns. A: The temporal lobe is being retracted to expose the skull base. B: The Sylvian fissure has been opened exposing the middle cerebral artery. C: The internal carotid is exposed between the optic chiasm (below) and the oculomotor nerve (above). D: Liliquist's membrane has been opened exposing the entire posterior communicating artery and the proximal posterior cerebral artery (below oculomotor nerve).

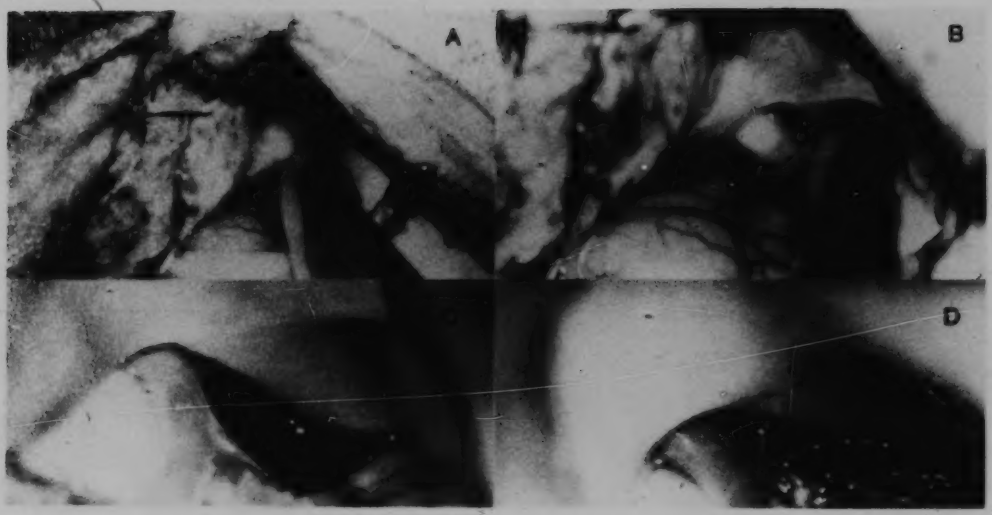

A
B
D

Figure 2

Induction of subarachnoid hemorrhage. A: Autologous blood clot has been placed around the exposed intracranial vessels. B: The middle fossa is filled with 4 ml of blood clot.

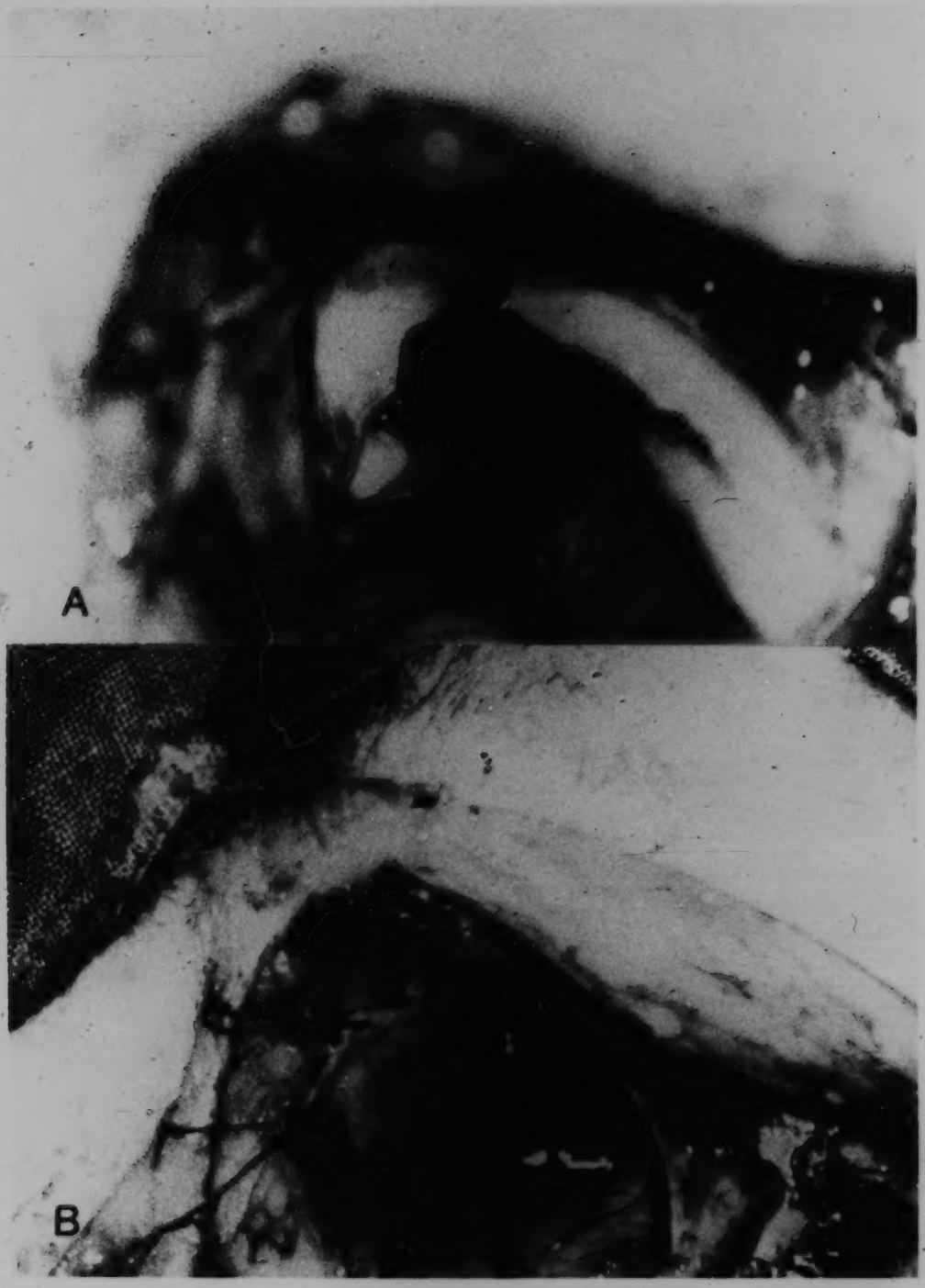

A
B

Figure 3

Insertion of Ommaya reservoir. A: The silicone catheter is placed in the region of the exposed vessels. B: The catheter is brought out through the dura and connected to an Ommaya reservoir (C) which is sutured superficial to the temporalis muscle beneath the scalp flap.

sutured to the temporalis muscle's fascia beneath the scalp flap (fig 3C). The dura, temporalis muscle, and scalp were closed in separate layers. The same procedure was then repeated on the left side. However, the Ommaya reservoir was placed only on the right side. The anesthesia was terminated in the same manner as described for baseline angiography.

INTRATHECAL NIMODIPINE ADMINISTRATION

Postoperatively, animals were observed daily for the development of a delayed ischemic neurological deficit. The treatment group received intrathecal nimodipine injections, 3 times per day for 6 post-operative days. Nimodipine was administered by percutaneous injection into the Ommaya reservoir over a 5 minute time period under light ketamine sedation (3 mg/kg, i.m.). Each injection consisted of 1 ml (0.2 mg) of soluble nimodipine [isopropyl - (2-methoxyethyl) - 1,4-dihydro-2,6-dimethyl-4(3-nitrophenyl) - 3,5-pyridinedicarboxylate] (10 mg / 50 ml ampulles, polyethylene glycol 400 / ethanol solvent, Miles Laboratories Inc., New Haven, Connecticut).

DAY 7 - ANGIOGRAPHY

On day 7 post-SAH induction, all animals underwent angiography in the same manner as described for the baseline angiogram. Following the day 7 angiogram under the same anesthetic, one-half of the animals in each group received a 1 ml intrathecal injection of nimodipine into the Ommaya reservoir and one-half of the animals in each group received a 1 ml intrathecal injection of placebo solvent. Two hours after the intrathecal injections a repeat day 7 angiogram was performed.

SACRIFICE

The sacrifice was performed on day 7 post-SAH induction under the same anesthetic as the angiography. Fifteen minutes prior to sacrifice, horseradish peroxidase (HRP)(80 mg/kg dissolved in 2 ml of normal saline) was injected into the Ommaya reservoir in order to evaluate the distribution of an intrathecally administered compound in this model.

Intraarterial perfusion was performed via a left ventricular cannula with the right atrium opened widely and the descending aorta ligated. Circulating

blood was washed out with 1 litre of normal saline solution under 110 mmHg pressure. This was followed by a 500 ml perfusion of fixation solution (2% glutaraldehyde and 2% formaldehyde in Millonig's buffer, 0.12 M, pH 7.4, at 4°C). The brain was removed and placed in fixative solution for a minimum of 6 hours.

The entire circle of Willis was dissected out under magnification and incubated in a saturated solution of 3,3'-diaminobenzidine (0.05 M) in Trix-HCL buffer, pH 7.6, and 0.01% H_2O_2. The HRP reactive products stained the vessels brown. Gross photographs were taken and the vessels then submitted for electron microscopy. All specimens were fixed for 1 hour in 1% osmium tetroxide in Millonig's buffer, 0.07 M, and sectioned for scanning electron microscopy (SEM) (Phillips 505 electron microscope; N.V. Phillips Gloeilampenfabrieken, Eindhoven, The Netherlands) and transmission electron microscopy (TEM) (Phillips Model 410).

DATA MEASUREMENTS AND ANALYSIS

Angiographic vessel diameters were measured at 12 points; bilateral cavernous carotid arteries (C3-ICA), bilateral supraclinoid internal carotid arteries (C4-ICA), bilateral anterior cerebral arteries (ACA),

bilateral proximal middle cerebral arteries (MCA), bilateral vertebral arteries (VA), proximal pericallosal artery (PCA), and the basilar artery in it's midsegment (BA). Measurements of each vessel were performed 6 times in a blinded fashion with a calibrated optical micrometer and mean values determined. A radiopaque control standard was used for correction of measurements to constant magnification.

All data were coded, entered into a computer, and edited. Data were analyzed using an analysis of variance with significance at the $p < 0.05$ level unless otherwise stated. Comparisons were made between baseline and day 7 angiograms within each group (paired t-test) and between the groups. Groups were compared at baseline to determine whether there was any difference at the onset of the study.

CHAPTER THREE: RESULTS

The animals in each group did not differ significantly in body weight, mean arterial blood pressure, heart rate, or $PaCO_2$ physiological parameters at baseline and day 7 measurements (Table 1). Therefore no adjustments using baseline values for covariates were required.

NEUROLOGICAL STATUS

All animals entered into the analysis were in excellent neurological condition following the angiographic and craniectomy procedures. No animal developed a delayed ischemic neurological deficit. All animals in the nimodipine treatment group showed a transient adverse effect following the intrathecal injection of 1 ml of nimodipine under ketamine sedation (3 mg/kg). This was characterized by sedation and hypoventilation, of a much greater degree than that evident by ketamine sedation alone. Within about 1 hour of the injection, the animals regained an alert level of consciousness without any further adverse effects. However, 1 animal suffered a respiratory arrest and died 2 hours after an intrathecal nimodipine injection on day 3 post-SAH induction. This resulted in a 12.5 % mortality for the nimodipine treatment group. Twenty-three monkeys survived to the day 7 sacrifice for complete analysis.

TABLE 1

MEASUREMENTS OF PHYSIOLOGICAL PARAMETERS
AND ANGIOGRAPHIC VESSEL CALIBER

PARAMETER		PRE-SAH	DAY 7 POST-SAH		
			SHAM	CLOT	CLOT + NIMODIPINE
no. of monkeys		24	8	8	7*
body weight (kg)		3.4±0.4	3.5±0.3	3.3±0.3	3.3±0.2
MABP (mmHg)		108±5	108±6	105±3	109±4
HR (per min)		145±19	148±15	151±0.6	142±14
$PaCO_2$		39.7±0.7	39.5±0.4	39.9±0.6	39.4±1.0
Vessel Caliber (mm)					
C3-ICA	rt	1.52±0.08	1.55±0.04	1.17±0.31	1.20±0.32
	lt	1.47±0.06	1.50±0.05	1.25±0.22	1.16±0.25
C4-ICA	rt	1.01±0.09	1.05±0.09	0.71±0.13	0.76±0.21
	lt	0.97±0.12	0.96±0.11	0.68±0.13	0.70±0.23
ACA	rt	0.76±0.08	0.78±0.08	0.48±0.07	0.51±0.15
	lt	0.72±0.06	0.71±0.06	0.50±0.08	0.50±0.09
MCA	rt	0.96±0.10	0.88±0.10	0.51±0.10	0.55±0.06
	lt	0.91±0.08	0.93±0.09	0.50±0.10	0.52±0.10
PCA		0.79±0.06	0.80±0.04	0.69±0.17	0.74±0.10
VA	rt	0.80±0.09	0.79±0.05	0.71±0.13	0.69±0.16
	lt	0.75±0.08	0.70±0.07	0.72±0.11	0.68±0.16
BA		1.01±0.09	0.95±0.05	0.87±0.17	0.90±0.19

values are means +/- standard error of the means

MABP: mean arterial blood pressure HR: heart rate
C3-ICA: cavernous internal carotid artery
C4-ICA: supraclinoid internal carotid artery
ACA: anterior cerebral artery
MCA: middle cerebral artery
PCA: proximal pericallosal artery
VA: vertebral artery, BA: basilar artery

* 1 animal died on day 3 following an intrathecal injection of nimodipine

PREVENTION OF ANGIOGRAPHIC VASOSPASM

Mean angiographic vessel caliber measurements in millimeters with standard deviations are given in table 1. Baseline measurements for each vessel did not differ significantly between the sham, clot, and clot plus nimodipine (tid) groups. Measurements between the right and left sides also did not differ significantly for each vessel at baseline or day 7.

The sham group showed no significant change in vessel caliber measurements between baseline and day 7 post-SAH induction. The clot group developed a decrease in vessel caliber from baseline in all vessels measured. However, statistical significance was not present for the vertebral and pericallosal arteries. The clot plus nimodipine group also developed a decrease in vessel caliber in all vessels measured with significance obtained in all vessels except the vertebral and pericallosal arteries. There was no significant difference in the day 7 angiograms between the clot and clot plus nimodipine groups.

Percentage change in vessel caliber from baseline measurement between the three groups is illustrated in figure 4. The right and left sided data have been

combined. There was no significant difference in reduction of vessel caliber between the clot and the clot plus nimodipine groups. The greatest reduction in vessel caliber occurred in the C4-ICA, ACA, and MCA vessels in the clot and clot plus nimodipine groups (28 to 45 % reduction, $p < 0.001$). The C3-ICA vessels averaged a 20 % reduction in vessel caliber from baseline in the clot and clot plus nimodipine groups ($p < 0.01$). The basilar arteries developed an average reduction in vessel caliber of 13 % ($p < 0.05$). The vertebral and pericallosal arteries were reduced in caliber an average of 10 %. Figure 4 also illustrates the absence of a significant change from baseline to day 7 in the sham group vessels.

The number of animals developing vasospasm of the MCA vessel in each group is shown in table 2. Extent of vasospasm was graded as mild (11 - 30 % reduction in vessel caliber), moderate (31 - 50 % ↓), and severe (> 50 % ↓). No animal in the sham group developed vasospasm. Three animals in the clot group developed severe vasospasm compared to 4 animals in the clot plus nimodipine group. Four animals in the clot group developed moderate spasm compared to 3 animals in the clot plus nimodipine group. Significant vasospasm

Figure 4

Bar graph of percentage change in vessel caliber from baseline for control and treatment groups. The left and right sided data have been combined for bilateral vessels. C3-ICA, cavernous internal carotid artery; C4-ICA, supraclinoid internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, proximal pericallosal artery; VA, vertebral artery; BA, basilar artery.

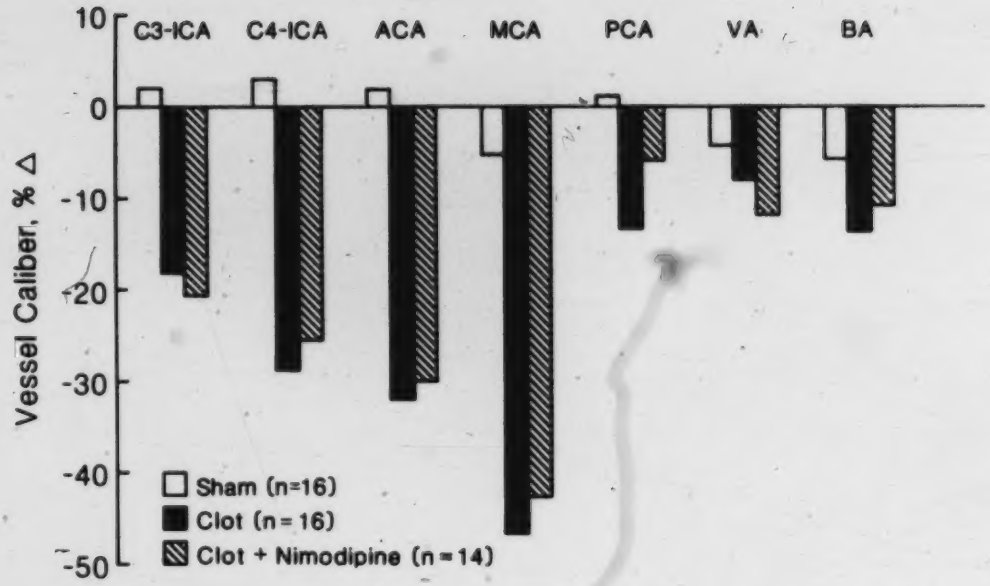

C3-ICA
C4-ICA
ACA
MCA
PCA
VA
BA
10
0
-10
-20
-30
-40
-50
Vessel Caliber, % Δ
Sham (n=16)
Clot (n=16)
Clot + Nimodipine (n=14)

TABLE 2

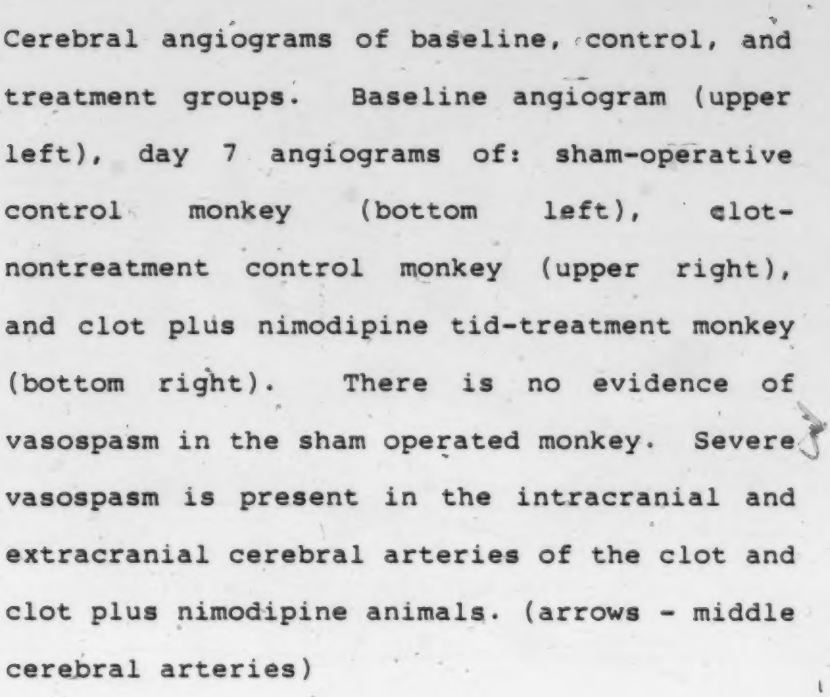
SEVERITY OF VASOSPASM IN CONTROL AND TREATMENTS GROUPS

GROUP	Number of Animals Developing Vasospasm (MCA) MILD	MODERATE	SEVERE
SHAM (n=8)	0	0	0
CLOT (n=8)	1	4	3
CLOT + NIMODIPINE (n=7*)	0	3	4

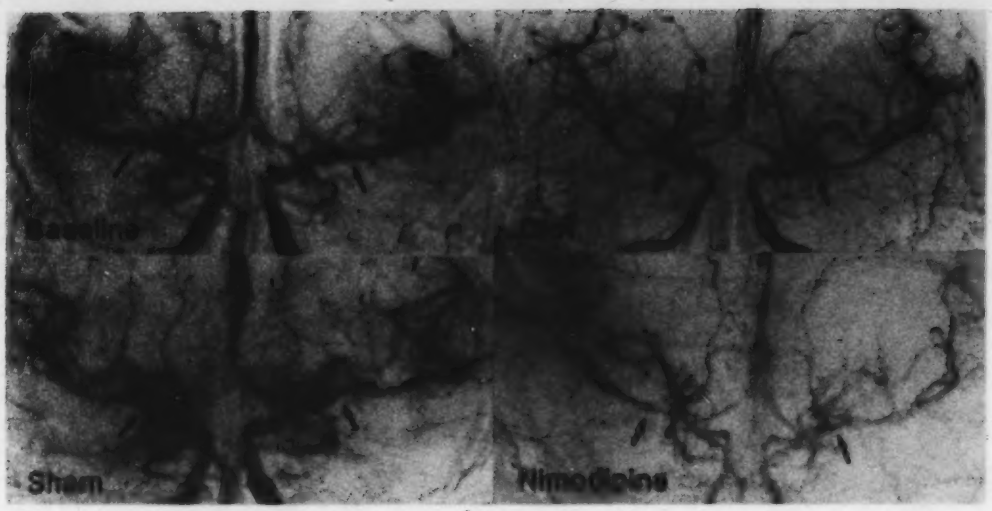
MCA: middle cerebral artery
mild: 11 - 30 % reduction in MCA vessel caliber
moderate: 31 - 50 % reduction
severe: > 50 % reduction

* 1 animal died on day 3 following an intrathecal injection of nimodipine

Figure 5



Cerebral angiograms of baseline, control, and treatment groups. Baseline angiogram (upper left), day 7 angiograms of: sham-operative control monkey (bottom left), clot-nontreatment control monkey (upper right), and clot plus nimodipine tid-treatment monkey (bottom right). There is no evidence of vasospasm in the sham operated monkey. Severe vasospasm is present in the intracranial and extracranial cerebral arteries of the clot and clot plus nimodipine animals. (arrows - middle cerebral arteries)


Sham
Nimodipine

(> 25 % ↓) was present in 100 % of animals with subarachnoid clot. Representative baseline and day 7 angiograms for the three groups are illustrated in figure 5.

TREATMENT OF CHRONIC VASOSPASM

Figure 6 illustrates the changes in vessel caliber measurements at day 7, before and after an intrathecal injection of nimodipine or placebo solvent. No significant differences were present between the right and left sided measurements of the baseline and day 7 angiograms, before and after the intrathecal injection. The right and left sided data were therefore combined. No significant differences were present between the day 7 post-SAH angiograms of the clot and clot plus nimodipine groups and therefore these data were also combined.

Mild reduction in vessel caliber from baseline was present for the C3-ICA vessel (19 % ↓, $p < 0.001$). Two hours following an intrathecal injection of nimodipine (1 ml - 0.2 mg), there was no significant dilation of the C3-ICA vessel. The basilar artery also showed a mild reduction in vessel caliber from baseline (21 % ↓, $p < 0.01$). However, following the intrathecal injection

of nimodipine, significant dilation ($p < 0.05$) occurred with the vessel caliber returning to the baseline value. More severe reduction in vessel caliber from baseline occurred in the ACA, C4-ICA, and MCA vessels (32-45% ↓, $p < 0.001$). No significant dilation occurred in these vessels after the intrathecal nimodipine injection. The placebo solvent injection (1 ml) was administered to a separate group of animals instead of nimodipine and did not result in any significant change in vessel caliber from the day 7 post-SAH angiogram.

The sham group showed no significant change in vessel caliber at baseline, day 7 post-SAH, day 7 post-intrathecal nimodipine, and day 7 post-intrathecal placebo solvent angiograms. The sham group vessels may have been near maximally dilated, detection of any further dilation after intrathecal nimodipine was not possible by angiography.

Representative angiograms at baseline, day 7 post-SAH, and following the intrathecal nimodipine injection are shown in figures 7 and 8. Figure 7 shows severe diffuse vasospasm at day 7 after SAH induction. No dilation of vessels occurred after the intrathecal nimodipine injection. This response was observed in 7 out of 8 animals with subarachnoid clot. However, 1

Figure 6

Line graph of change in mean vessel caliber of cerebral arteries from baseline (n=30) to day 7 post-SAH induction (n=30) and 2 hours following an intrathecal injection of nimodipine (n=16) or placebo solvent (n=14). Measurements of baseline and day 7 angiograms for clot and clot plus nimodipine groups have been combined. Left and right sided data have also been combined. C3-ICA, cavernous internal carotid artery; BA, basilar artery; C4-ICA, supraclinoid internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

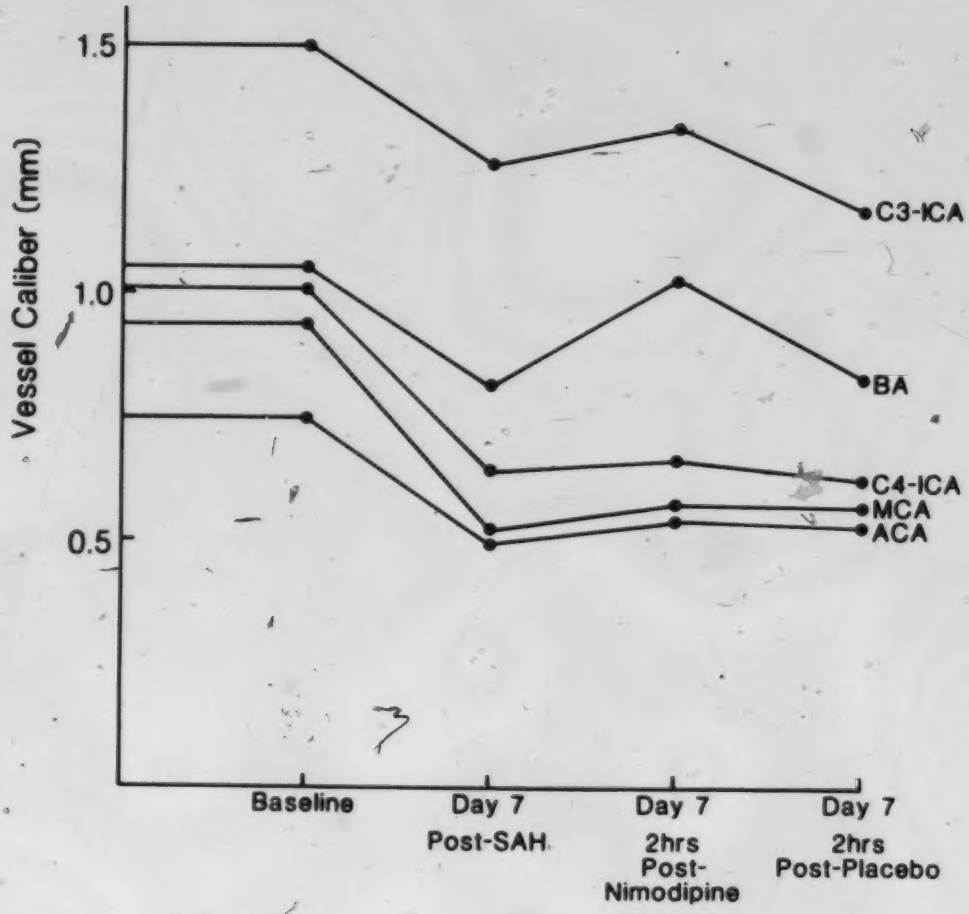

1.5
1.0
0.5
Vessel Caliber (mm)
C3-ICA
BA
C4-ICA
MCA
ACA
Baseline
Day 7
Post-SAH
Day 7
2hrs
Post-
Nimodipine
Day 7
2hrs
Post-Placebo

Figure 7

Baseline angiogram of a clot group monkey (upper), day 7 post-SAH angiogram (middle), and day 7 post-intrathecal nimodipine injection (lower). Severe vasospasm is present at day 7 post-SAH induction with no dilation of vessels occurring after an intrathecal nimodipine injection. Seven out of 8 animals showed this response to an intrathecal nimodipine injection. (large arrows - middle cerebral arteries, small arrows - basilar arteries)

Baseline
2hrs Post-Nimodipine

Figure 8

Baseline angiogram of a clot group monkey (upper), day 7 post-SAH angiogram (middle), and day 7 post-intrathecal nimodipine injection (lower). Severe vasospasm is present at day 7 post-SAH induction with marked dilation of vessels and almost complete reversal of vasospasm after an intrathecal nimodipine injection. Only 1 out of 8 animals showed this response. (large arrows - middle cerebral arteries, small arrows - basilar arteries)

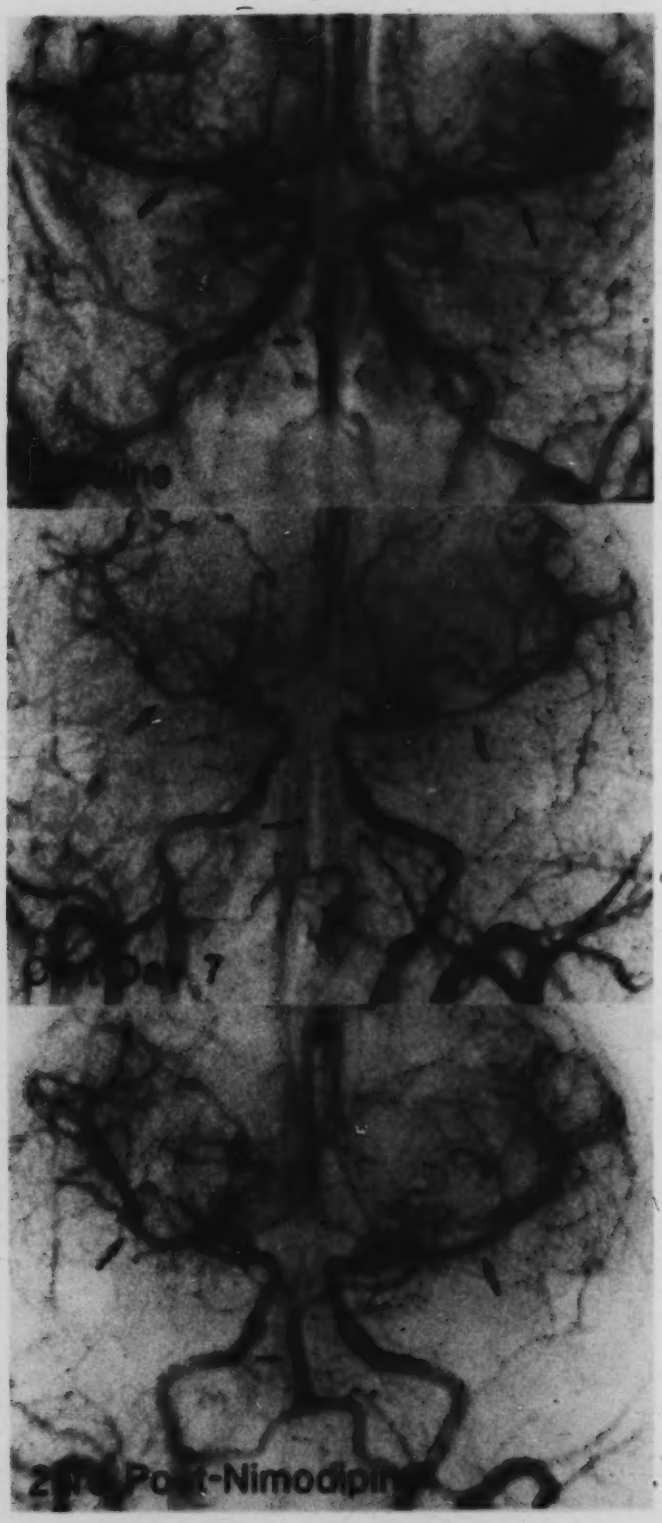
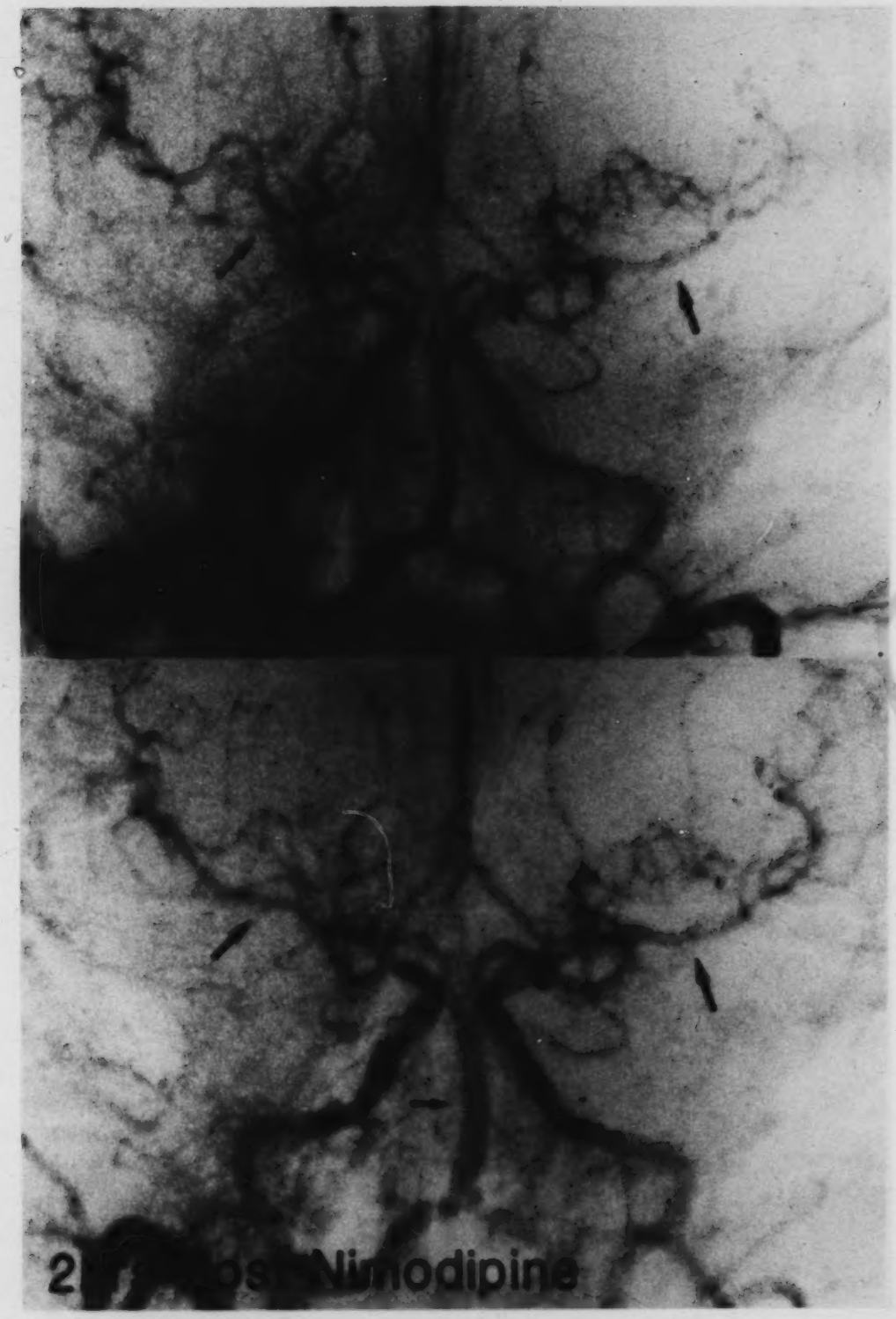


Figure 9

Day 7 post-SAH angiogram of a clot group monkey (upper) and day 7 post-intrathecal nimodipine injection (lower). Severe vasospasm is present in the middle cerebral arteries (large arrows) with no significant dilation occurring after an intrathecal nimodipine injection. Mild vasospasm is present in the basilar artery (small arrow) with significant dilation occurring after intrathecal nimodipine. Three out of 8 animals showed this isolated response of the basilar artery to nimodipine.


2
Nimodipine

animal developed marked diffuse vasodilation with nearly complete reversal of vasospasm following the intrathecal injection of nimodipine (fig 8). Three other animals in this group developed only dilation of the basilar artery with complete reversal of mild spasm in this vessel after the intrathecal nimodipine injection (fig 9). Vessels in moderate and severe spasm did not significantly dilate in these animals.

PATHOLOGY

Horseradish peroxidase reactive products stained the entire circle of Willis brown in all groups following administration of HRP into the Ommaya reservoir (fig 10).

Scanning and transmission electron microscopy showed pathological changes of chronic vasospasm in the clot and clot plus nimodipine groups; characterized by vessel wall thickening, a convoluted endothelial surface, disruption of endothelial tight junctions, and myonecrosis of the tunica media. Dramatic contrast to the sham-operated normal vessels is evident in figures 11 to 14.

Adverse gross and light microscopic cerebral abnormalities different from those noted in the control animals were not observed in the animals treated with intrathecal nimodipine postoperatively.

Figure 10

Cerebral vessel staining by HRP. The circle of Willis in a monkey with subarachnoid blood clot is diffusely stained brown (left) following administration of intrathecal horseradish peroxidase (HRP) via the Ommaya reservoir. Control vessels (right) of another monkey without HRP administration.

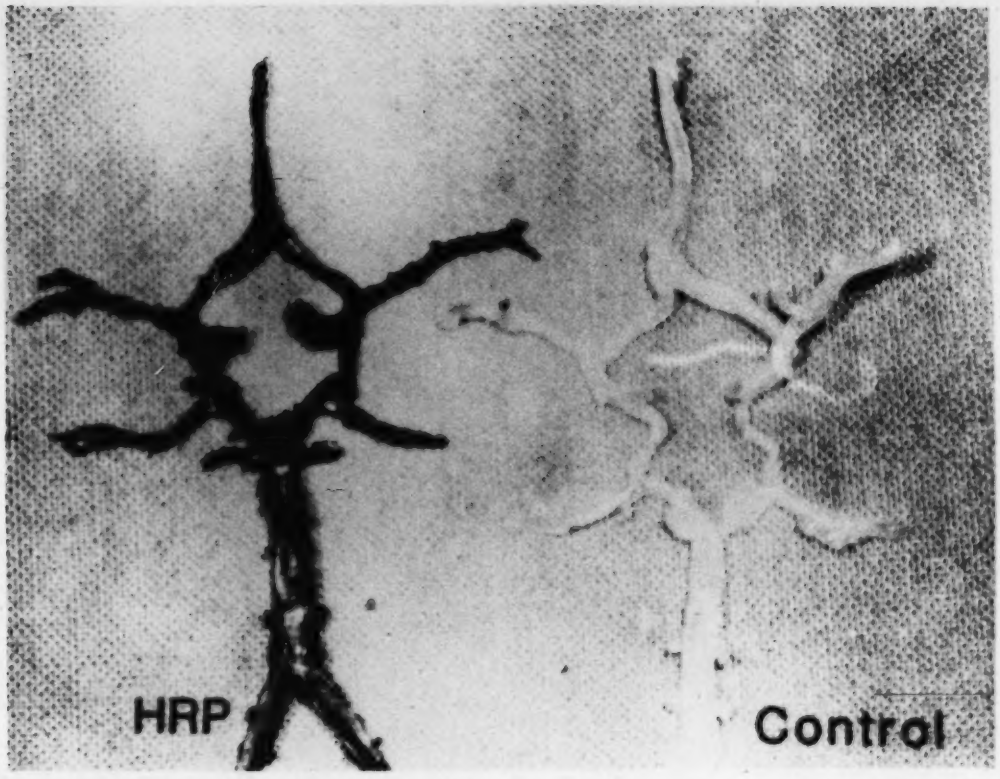

HRP
Control

Figure 11

Scanning electron microscopy showing the middle cerebral artery lumens of sham (upper), clot (middle), and clot plus nimodipine (lower) monkeys. The arterial wall of the sham monkey is normal. Vessel wall thickening and a convoluted endothelial surface is present in the vessels of the clot and intrathecal nimodipine groups. X36

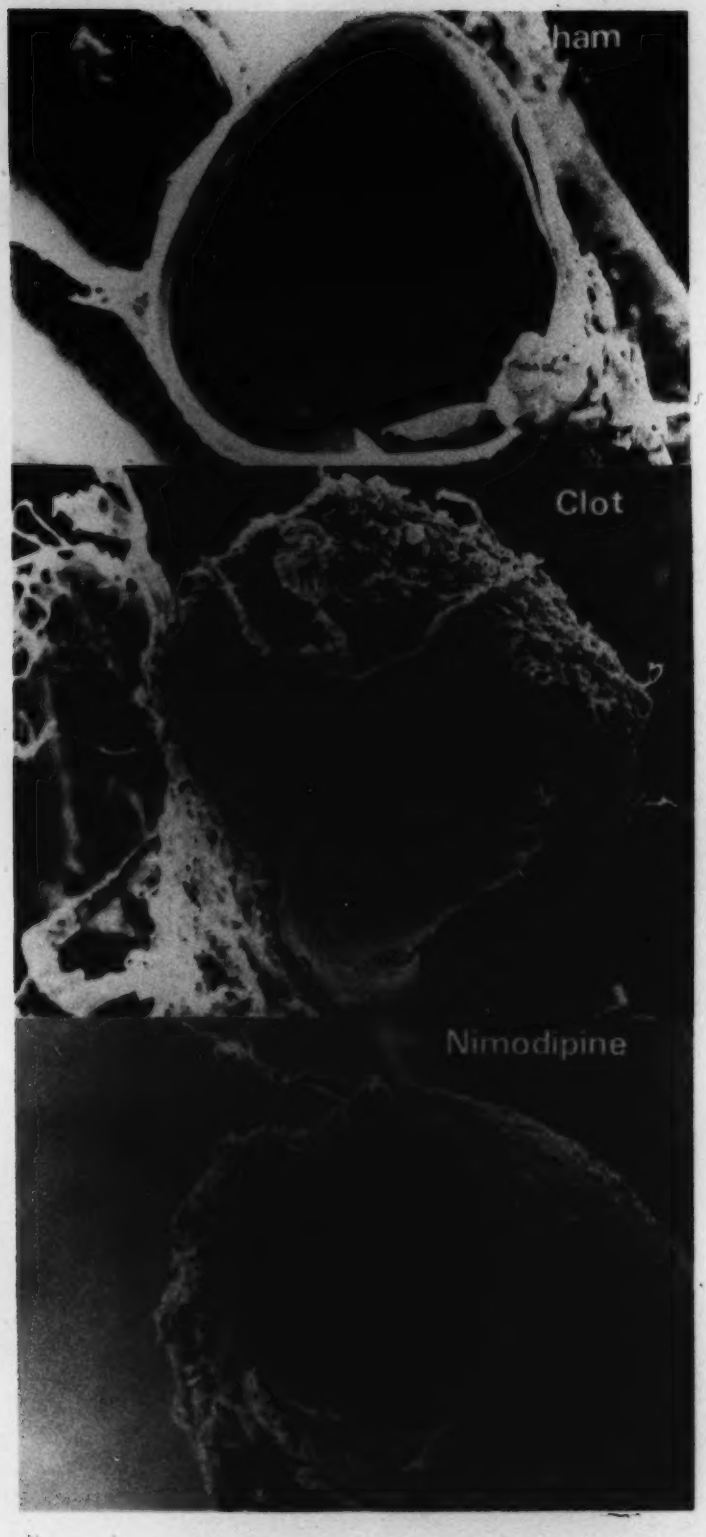
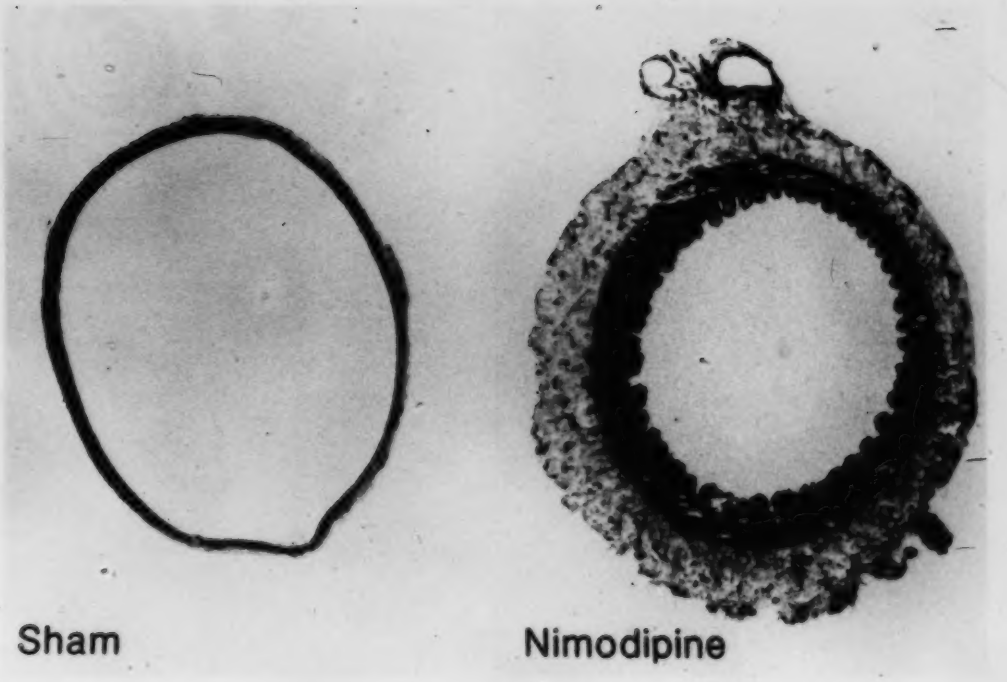

ham
Clot
Nimodipine

Figure 12

Histological sections of vessels from sham and nimodipine groups. Marked contrast is present between the two groups with regard to the thickness of the vessel wall, and folding of the internal elastic lamina. (1 micron thick sections embedded in epoxy resin and stained with methylene blue) X 100



Sham

Nimodipine

Figure 13

Histological sections of vessels from sham and nimodipine groups at higher magnification than fig. 12. Note the linear shape of the smooth muscle cells and internal elastic lamina of the normal sham vessel, compared to the more circular shape of the smooth muscle cells and convoluted internal elastic lamina in the contracted vessel of the nimodipine group. X 250

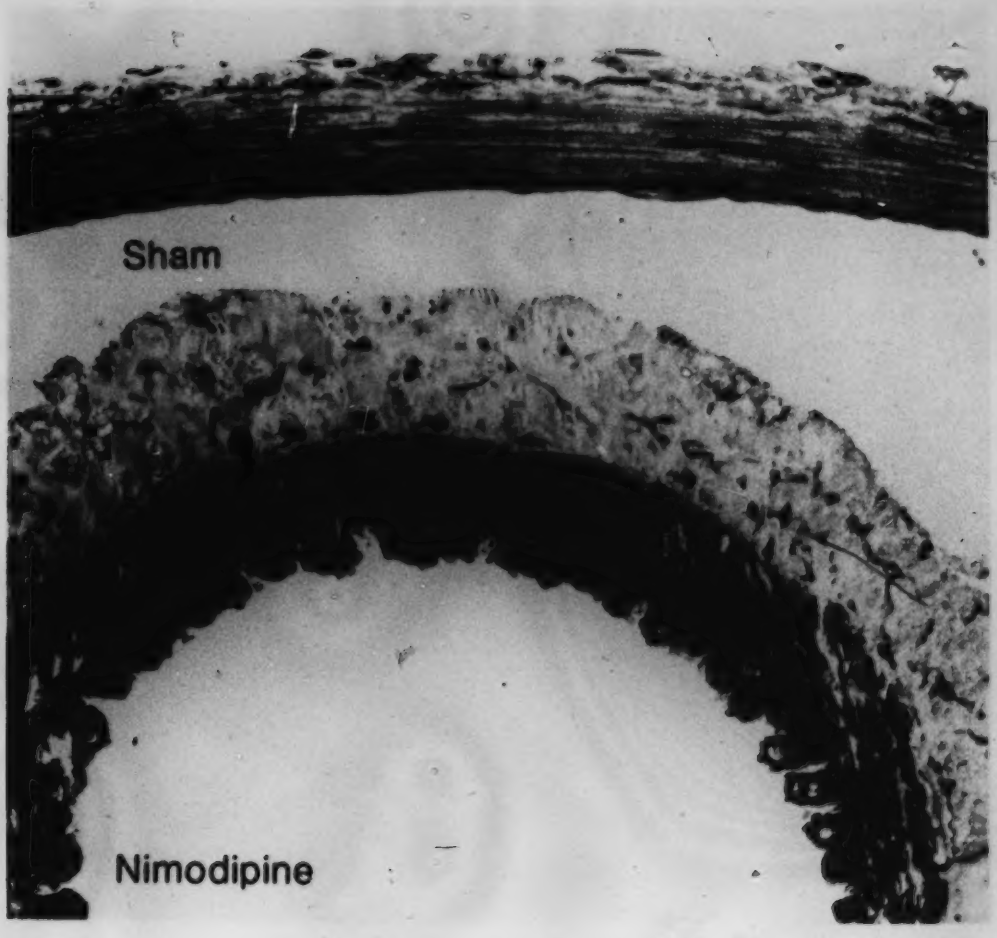
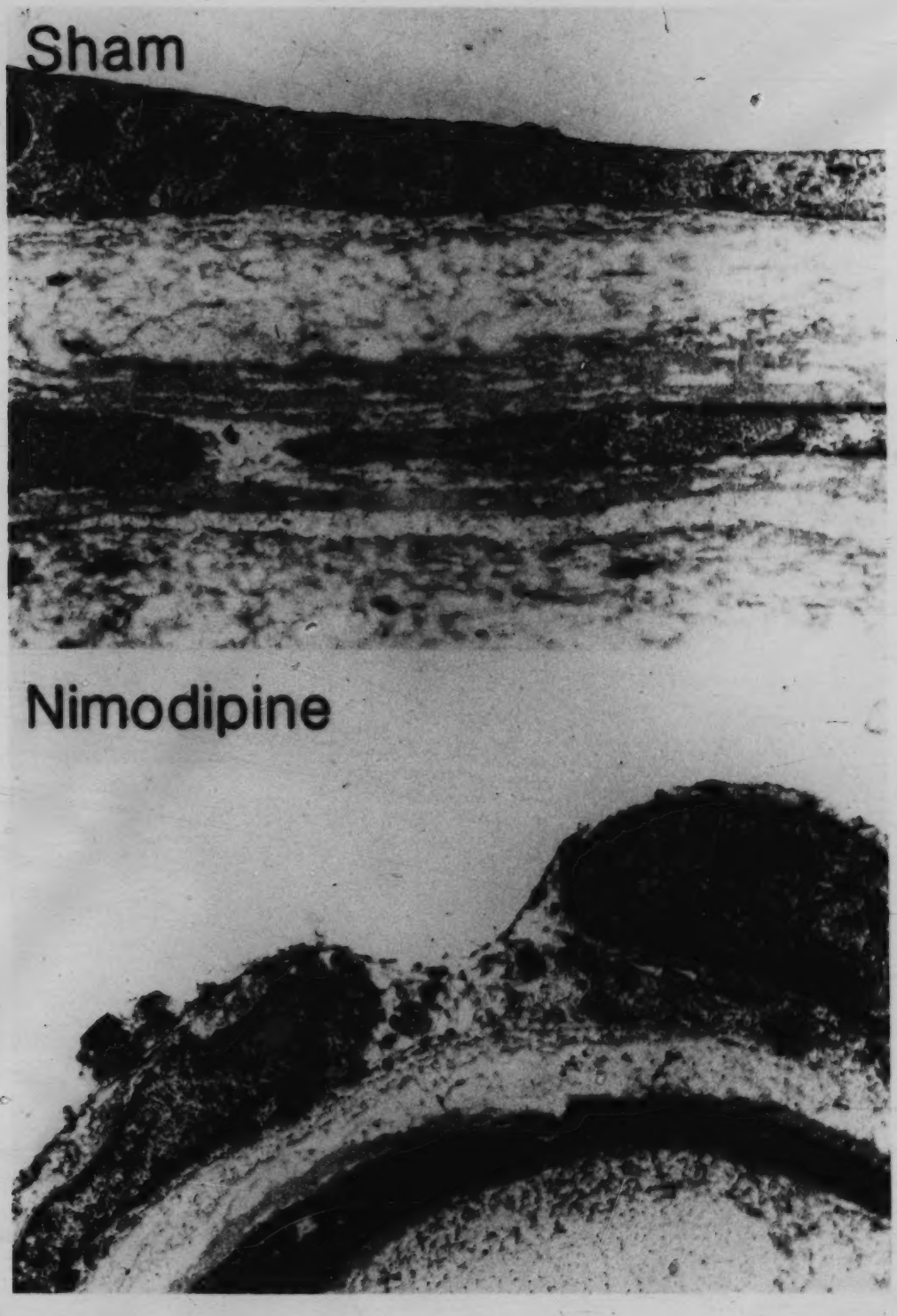

Sham
Nimodipine

Figure 14

Transmission electron microscopy of sham and nimodipine groups. Note the normal endothelial cells with an intact tight junction between the cells of the sham vessel, in contrast to the disrupted tight junction between damaged endothelial cells of the nimodipine group. X 12,320


Sham
Nimodipine

CHAPTER FOUR: DISCUSSION

The present study was unable to show any benefit of intrathecal nimodipine therapy in preventing angiographic vasospasm or pathological changes of chronic vasospasm in the primate model of subarachnoid hemorrhage. Reversal of established angiographic vasospasm did not occur in vessels which were in moderate or severe spasm (87.5 % of animals). Only 1 animal in 8 with subarachnoid blood clot showed a significant diffuse vasodilatory response to intrathecal nimodipine. Only the basilar artery showed reversal of mild angiographic vasospasm in 37.5 % of animals.

Consideration of the reasons for the negative findings in this study should include: possible inadequate dosage of intrathecal nimodipine; lack of patency of the Ommaya reservoir delivery system; limited extent of nimodipine diffusion in the CSF and inadequate contact with the cerebral vessels; failure of penetration of nimodipine to the vessel media; and nimodipine's possible lack of effect on vessels with the pathological changes of chronic vasospasm and the degree of vasospasm produced in this model.

Although dose-response curves of intrathecal nimodipine are not available, the dosage chosen in this

study (0.2 mg/1 ml) was based on the same dosage used in Auer's clinical study which showed a positive response in 9 of 12 patients (16). However, only 4 of those 9 patients showed evidence of angiographic vasospasm prior to the intrathecal nimodipine treatment and no patient was symptomatic from vasospasm. The degree of vasospasm in this clinical study must therefore be considered mild. Gioia et al. (60) used a higher concentration of intrathecal nimodipine (0.419 mg/ml) in the single and two-hemorrhage canine model of vasospasm. This produced a prompt and complete reversal of cerebral vasospasm in all groups. The maximum dilating effect appeared to occur at 2 hours after nimodipine treatment but disappeared by 24 hours. A concentration of 0.0419 mg/ml was without significant effect and these investigators considered the intrathecal threshold dose to be between the two dose ranges tested. The degree of vasospasm produced in the above canine models ranged from 25 to 40 % reduction in basilar artery caliber, 1 to 5 days after SAH induction. In the multi-hemorrhage canine model, Zabramski et al. (202) produced more severe vasospasm (average 71 % reduction in basilar artery caliber from baseline to day 7 post-SAH induction). This was only partially reversed by an intracisternal

injection of nimodipine (0.1 mg/ml), in 4 out of 6 dogs (average 15 % dilation from post-SAH angiogram). It is reasonable to consider that an optimal dosage of intrathecal nimodipine exists, however the results of the previous studies suggest that severity of vasospasm was a more important factor in determining positivity of a response to intrathecal nimodipine. This was suggested in our study, in which vessels in moderate or severe spasm (C4-ICA, ACA, MCA) did not dilate, unlike vessels in mild spasm (basilar artery).

Despite a partially blocked catheter in some cases and a subarachnoid space packed with blood clot, HRP was still able to circulate in the CSF and contact all the blood vessels in a diffuse manner, since they were all stained brown. This provides indirect evidence for the adequate distribution of intrathecal nimodipine in this study, since nimodipine is a much smaller molecule (m[illegible] weight: 419) than HRP (molecular weight: 40,000).

Zervas et al. (204) and Espinosa et al. (44) have noted an absence of vasa vasorum of intracranial vessels in experimental studies. Adventitial stomas have been identified on normal intracranial arteries which may provide a morphological communication of CSF with smooth

muscle cells of the tunica media and provide a pathway in the adventitia for nourishment of cerebral vessels, analogous to systemic vasa vasorum. Espinosa et al. (44) have identified blocked stomas by well-organized blood clots on the adventitial surface and suggest a disturbance of vessel wall nutrition which may aggravate vasospasm. Vessel wall penetration of an intrathecally administered compound may also be impaired in a similiar manner.

In vitro studies on reactivity of cerebral vessels to vasocontrictor substances (5-hydroxytryptamine, norepinephrine, and potassium chloride) have shown a highly significant reduction in reactivity for vessels in chronic vasospasm (91,181). Intrinsic reactivity disturbances to vasodilator substances may also exist in these vessels.

Pathological evidence of adverse effects of intrathecal nimodipine such as extensive leptomeningeal fibrosis, meningitis, cerebral infarction, etc. were not present in this study. The transient adverse clinical effects appeared related to a potentiation of the sedative effect of ketamine. Intrathecal injections of nimodipine were performed under light ketamine sedation (3 mg/kg) using a small volume of nimodipine and a

prolonged injection time (1 ml over 5 min). Pupillary abnormalities were not observed and recovery from sedation ocurred within 1 hour, except for the one animal which developed excessive hypoventilation and died from a respiratory arrest. Therefore, raised intracranial pressure complicating the intrathecal injections appears unlikely. A direct sedative effect on the brain appears more probable.

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

Vasodilator medication has received the most extensive investigation for therapy of chronic cerebral vasospasm compared to all other treatment modalities. A consistently effective vasodilator has not been found to prevent or reverse chronic angiographic cerebral vasospasm, despite the fact that potent cerebral selective vasodilators have been tried. Various dosages and routes of administration of these vasodilators have been tried with no consistently beneficial effect on angiographic vasospasm. This has been the experience of the neurovascular laboratory in which the present study was performed using intrathecal nimodipine. Previous to this study, systemic administration was not found to be effective at escalating dosages of nimodipine in the primate model (43,123).

Pharmacological vasodilation of chronic cerebral vasospasm has obviously been a very difficult thing to accomplish and the question of whether or not chronic vasospasm is acutely reversible remains unanswered. Controversy still exists as to the nature of chronic vasospasm. Is it a chronic contraction of smooth muscle cells or a proliferative vasculopathy with constriction of the vessel wall? However, the fact that

morphological damage to the vessel wall does occur in chronic vasospasm is undisputed. Also, the fact that subarachnoid clot causes chronic vasospasm is undisputed. Perhaps it is time to focus much less attention on the search for a specific etiological vasoconstricting substance in the subarachnoid clot and pharmacological antagonism of that substance(s), and focus more attention on studying safe, effective modalities of subarachnoid clot removal.

Early and complete surgical removal of subarachnoid clot has been shown to prevent angiographic vasospasm in the primate model (66,124). Perhaps adjunctive therapy with intrathecal fibrinolytic agents will facilitate clot lysis and washout in the clinical situation where complete mechanical clot removal is more difficult. An experimental trial in the primate model is warranted before clinical investigation in view of the potential adverse effects.

Angiographic vasospasm does not necessarily indicate that cerebral infarction and a poor outcome will occur. Prevention and treatment of symptomatic vasospasm (ie. delayed ischemic neurological deficits) with early aneurysm operation, volume expansion, induced hypertension, and/or systemic nimodipine therapy

improves clinical outcome (7,15,87,96). The mechanism of nimodipine's beneficial effect is unknown, but may be related to a protective effect on the brain by dilating small arterioles (not angiographically visible) and improving collateral cerebral blood flow during cerebral ischemia. A direct neuronal protective effect during cerebral ischemia is also a possibility. Further investigation with advanced technology for quantitating cerebral blood flow and metabolism is therefore warranted for calcium antagonist medications despite the fact that a significant effect on angiographic vasospasm has not been shown with these agents. Many neurosurgeons have stopped worrying about angiographic vasospasm and have concentrated their efforts on symptomatic vasospasm.

Although the primate model of chronic vasospasm is the best animal model, it has not produced delayed ischemic deficits to the same degree that is observed clinically. Extension of the unilateral clot placement over the anterior circulation to a bilateral clot placement over the anterior and posterior circulations increased the incidence of delayed ischemic deficits to 25 % in one study with 8 control animals (124). However, the present study using the same bilateral clot

placement model resulted in no delayed ischemic deficits in another 8 control animals. More research on improving the primate model therefore appears indicated.

Advances in knowledge of chronic cerebral vasospasm have been made over the past 20 years. However, the advances have not been rapid. The literature is muddled with poor clinical and experimental studies. Uncontrolled clinical trials and experimental studies on inferior animal models have repeatedly suggested various etiologies and effective treatment modalities which have been disputed in other studies. Multi-centre, controlled clinical trials and experimental studies on primates are considered gold standard studies. The proportion of these studies in the literature compared to uncontrolled clinical trials and non-primate experimental studies is surprisingly low. The most important recommendation of this thesis is for proportionately more gold standard studies on chronic cerebral vasospasm.

BIBLIOGRAPHY

1 Acheson RM, Williams DRR: Epidemiology of cerebrovascular disease: Some unanswered questions, in: Rose' FC (ed): Clinical Neuroepidemiology. Tunbridge Wells: Kent, 'Pitman Medical, 1980, pp. 88-104.

2 Alexander III E, Black PM, Liszczak TM, Zervas NT: Delayed CSF lavage for arteriographic and morphological vasospasm after experimental SAH. J Neurosurg 63:949-958, 1985.

3 Alknse JF, Branson PJ: Prevention of experimental subarachnoid hemorrhage-induced arterial vaso-necrosis with phosphodiesterase inhibitor phthalazinol (EG-626). Stroke 10:638-644, 1979.

4 Alksne JF, Branson PJ, Bailey M: Modification of experimental post-subarachnoid hemorrhage vasculopathy with intracisternal plasmin. Neurosurgery 19:20-25, 1986.

5 Alksne JF, Greenhoot JH: Experimental catecholamine-induced chronic cerebral vasospasm. Myonecrosis in vessel wall. J Neurosurg 41:440-445, 1974.

6 Allcock JM, Drake CG: Ruptured intracranial aneurysms - the role of arterial spasm. J Neurosurg 22:21-29, 1965.

7 Allen GS, Ahn MS, Preziosi TJ, Battye R, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB, Dorsey FC, Ingram CR, Mellits DE, Bertsch LA, Boisvert D, Hundley MB, Johnson RK, Strom JOA, Transou CR: Cerebral arterial spasm: A controlled trial of nimodipine in subarachnoid hemorrhage patients. N Engl J Med 308:619-624, 1983.

8 Allen GS, Bahr AL: Cerebral arterial spasm: Part 10. Reversal of acute and chronic spasm in dogs with orally administered nifedipine. Neurosurgery 4:43-47, 1979.

9 Allen GS, Banghart SB: Cerebral arterial spasm: Part 9. In vitro effects of nifedipine on serotonin-, phenylephrine-, and potassium-induced contractions of canine basilar and femoral arteries. Neurosurgery 4:37-42, 1979.

10 Allen GS, Gold LHA, chou SN, French LA: Cerebral arterial spasm. Part 3: In vivo intracisternal production of spasm by serotonin and blood and its reversal by phenoxybenzamine. J Neurosurg 40:451-458, 1974.

11 Allen GS, Henderson LM, Chou SN, French LA: Cerebral arterial spasm. Part 1: In vitro contractile activity of vasoactive agents on canine basilar and middle cerebral arteries. J Neurosurg 40:433-441, 1974.

12 Allen GS, Henderson LM, Chou SN, French LA: Cerebral arterial spasm. Part 2: In vitro contractile activity of serotonin in human serum and CSF on the canine basilar artery, and its blockade by phenoxybenzamine. J Neurosurg 40:442-450, 1974.

13 Arseni C, Maretsis M, Horvath L: Posttraumatic intracranial arterial spasm; Report of three cases. Acta Neurochir (Wien) 24: 25-35, 1971.

14 Asano T, Tanishima T, Sasaki T, Sano K: Possible participation of free radical reactions initiated by clot lysis in the pathogenesis of vasospasm after subarachnoid hemorrhage, in: Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore: Williams & Wilkins, 1980, pp. 190-201.

15 Auer LM: Acute operation and preventive nimodipine improve outcome in patients with ruptured cerebral aneurysms. Neurosurgery 15:57-65, 1984.

16 Auer LM: Preventive nimodipine and acute aneurysm surgery. Heading for the control of complications after aneurysmal subarachnoid hemorrhage. Neurochir 28:87-92, 1985.

17 Barry KJ, Gogjian MA, Stein BM: Small animal model for investigation of subarachnoid hemorrhage and cerebral vasospasm. Stroke 10:538-541.

18 Bergvall U, Galera R: Time relationship between subarachnoid hemorrhage, arterial spasm, changes in cerebral circulation and posthemorrhagic hydrocephalus. Acta Radiol (Diagn) 9:229-237, 1969.

19 Black PM: Hydrocephalus and Vasospasm after subarachnoid hemorrhage from ruptured intracranial aneurysms. Neurosurgery 18:12-16, 1986.

20 Blumenkopf B, Wilkins RH, Feldman JM: Cerebral vasospasm despite administration of reserpine and kanamycin. Neurosurgery 4:548, 1979.

21 Bolton TB: Mechanisms of action of transmitters and other substances on smooth muscle. Physiol Rev 59:606-717, 1979.

22 Boullin DJ, Brandt L, Ljunggren B, Tagari P: Vasoconstrictor activity in cerebrospinal fluid from patients subjected to early surgery for ruptured intracranial aneurysms. J Neurosurg 55:237-245, 1981.

23 Boullin DJ, Bunting S, Blaso WP, Hunt TM, Moncada S: Responses of human and baboon arterties to prostaglandin endoperoxides and biologically generated and synthetic prostacyclin: Their relevance to cerebral arterial spasm in man. Br J Clin Pharmac 7:139-147, 1979.

24 Brandt L, Ljunggren B, Anderson KE, Hindfelt B, Teasdale G: Vasoconstrictive effects of human post-hemorrhagic cerebrospinal fluid on cat pial arterioles in situ. J Neurosurg 54:351-356, 1981.

25 Brandt L, Andersson KE, Edvinsson L, Ljunggren B: Effects of extracellular calcium and of calcium antagonists on the contractile responses of isolated human pial and mesenteric arteries. J Cereb Blood Flow Metab 1:339-347, 1981.

26 Brown FD, Hanlon K, Mullan S: Treatment of aneurysmal hemiplegia with dopamine and mannitol. J Neurosurg 49:525-529, 1978.

27 Camp PE, Paxton HD, Buchan CG, Gahbauer H: Vasospasm after trans-spenoidal hypophysectomy. Case Report. Neurosurgery 7:382-386, 1980.

28 Cardoso ER, Peterson EW: Pituitary apoplexy and vasospasm. Surg Neurol 20:391-395, 1983.

29 Chapleau CE, White RP: Effects of prostacyclin on the canine isolated basilar artery. Prostaglandins 17:573-580, 1979.

30 Chyatte D, Rusch N, Sundt TM: Prevention of chronic experimental cerebral vasospasm with ibuprofen and high-dose methylprednisolone. J Neurosurg 59:925-932, 1983.

31 Chyatte D, Sundt TM: Response of chronic experimental cerebral vasospasm to methyl-prednisolone and dexamethasone. J Neurosurg 60:923-926, 1984.

32 Conway LW, McDonald LW: Structural changes of the intradural arteries following subarachnoid hemorrhage. J Neurosurg 37:715-723.

33 Crompton MR: The pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms. Brain 87:491-510, 1964.

34 Doczi T, Ambrose J, O'Laoire S: Significance of contrast enhancement in cranial computerized tomography after subarachnoid hemorrhage. J Neurosurg 60:335-342, 1984.

35 Drake CG: Management of cerebral aneurysm. Stroke 12:273-283, 1981.

36 Duff TA, Scott G, Feilbach JA: Ultrastructural evidence of arterial denervation following experimental subarachnoid hemorrhage. J Neurosurg 64:292-297, 1986.

37 Echlin FA: Spasm of basilar and vertebral arteries caused by experimental subarachnoid hemorrhage. J Neurosurg 23:1-11, 1965.

38 Ecker A, Riemenschneider PA: Arteriographic demonstration of spasm of the intracranial arteries with special reference to saccular arterial aneurysms. J Neurosurg 8:660-667, 1951.

39 Ellis EF, Nies AS, Oates JA: Cerebral arterial smooth muscle contraction by thromboxane A_2. Stroke 8:480-482, 1977.

40 Endo S, Suzuki J: Experimental cerebral vasospasm after subarachnoid hemorrhage. Participation of adrenergic nerves in cerebral vessel wall. Stroke 10:703-711, 1979.

41 Espinosa F: A primate model of chronic cerebral vasospasm: Development and application in the treatment of subarachnoid hemorrhage in humans. PhD Thesis, University of Alberta, 1985.

42 Espinosa F, Weir B, Boisvert D, Overton T, Castor W: Chronic cerebral vasospasm after large subarachnoid hemorrhage in monkeys. J Neurosurg 57:224-232, 1982.

43 Espinosa F, Weir B, Overton T, Castor W, Grace M, Boisvert D: A randomized placebo-controlled double-blind trial of nimodipine after SAH in monkeys. Part 1: Clinical and radiological findings. J Neurosurg 60:1167-1175, 1984.

44 Espinosa F, Weir B, Shnitka T: Electron microscopy of simian cerebral arteries after subarachnoid hemorrhage and after the injection of horseradish peroxidase. Neurosurgery 19:935-945, 1986.

45 Espinosa F, Weir B, Shnitka T, Overton T, Boisvert D: A randomized placebo-controlled double-blind trial of nimodipine after SAH in monkeys. Part 2: Pathological findings. J Neurosurg 60:1176-1185, 1984.

46 Edvinsson L, Brandt L, Andersson KE, Bengtsson B: Effect of a calcium antagonist on experimental constriction of human brain vessels. Surg Neurol 11:327-330, 1979.

47 Farrar JK: Chronic cerebral arterial spasm. The role of intracranial pressure. J Neurosurg 43:408-417, 1975

48 Farrar JK, Roach MR: The effects of increased intracranial pressure on flow through major cerebral arteries in vitro. Stroke 4:795-806, 1973.

49 Fein JM: Unruptured aneurysms and cerebral vasospasm, in: Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore: Williams & Wilkins, 1980, pp. 499-504.

50 Fein JM, Flor WJ, Cohan SL, Parkhurst J: Sequential changes of vascular ultrastructure in experimental cerebral vasospasm. Myonecrosis of subarachnoid arteries. J Neurosurg 41:49-58.

51 Finn SS, Stephensen SA, Miller CA, Drobnich L, Hunt WE: Observations on the perioperative management of aneurysmal subarachnoid hemorrhage. J Neurosurg 65:48-62, 1986.

52 Fisher CM, Kistler JP, David JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 6:1-9, 1980.

53 Flaim SF, Zelis R: Calcium channel blockers: Mechanisms of action and clinical applications. Baltimore, Urban & Schwarzenberg, 1982.

54 Flamm ES, Kim J, Lin J, Ransohoff J: Phosphodiesterase inhibitors and cerebral vasospasm. Arch Neurol 32:569-571, 1975.

55 Flamm ES, Ransohoff J: Treatment of cerebral vasospasm by control of cyclic adenosine monophosphate. Surg Neurol 6:223-229, 1976.

56 Fletcher TM, Traveras JM, Pool JL: Cerebral vasospasm in angiography for intracranial aneurysms: incidence and significance in one hundred consecutive angiograms. Arch Neurol 1:38-47, 1959.

57 Fodstad H, Forssell A, Liliequist B, Schannong M: Antifibrinolysis with tranexamic acid in aneurysmal subarachnoid hemorrhage: A consecutive controlled clinical trial. Neurosurgery 8:158-165, 1981.

58 Fraser RAR, Stein BM, Barrett RE, Pool JL: Noradrenergic mediation of experimental cerebrovascular spasm. Stroke 1:356-362, 1970.

59 Fukumori T, Tani E, Maeda Y, Sukenaga A: Effects of prostacyclin and indomethacin on experimental delayed cerebral vasospasm. J Neurosurg 59:829-834, 1983.

60 Gioia AE, White RP, Bakhitian B, Robertson JT: Evaluation of the efficacy of intrathecal nimodipine in canine models of chronic cerebral vasospasm. J Neurosurg 62:721-728, 1985.

61 Graf CJ: Results of direct attack on nonfistulous intracranial aneurysms with remarks on statistics. J Neurosurg 12:146-153, 1955.

62 Graham DI, MacPherson P, Pitts LH: Correlation between angiographic vasospasm, hematoma, and ischemic brain damage following SAH. J Neurosurg 59:223-230, 1983.

63 Grotenhuis JA, Bettag W, Fiebach O, Dabir K: Intracarotid slow bolus injection of nimodipine during angiography for treatment of cerebral vasospasm after SAH. J Neurosurg 61:231-240, 1984.

64 Grubb RL, Raichle ME, Eichling JO, Gado MH: Effects of subarachnoid hemorrhage on cerebral blood volume, blood flow, and oxygen utilization in humans. J Neurosurg 46:446-453.

65 Hagen AA, White RP, Robertson JT: Synthesis of prostaglandins and thromboxane B_2 by cerebral arteries. Stroke 10:306-309, 1979.

66 Handa Y, Weir B, Nosko M, Mosewich R, Tsuji T, Grace M: The effect of timing of clot removal on chronic vasospasm in a primate model. Submitted for publication to J Neurosurg, 1987.

67 Handa J, Yoneda S, Matsuda M, Handa H: Effects of prostaglandins A_1, E_1, E_2, and F_2 on the basilar artery of cats. Surg Neurol 2:251-255, 1974.

68 Hara H, Nosko M, Weir B: Cerebral perivascular nerves in subarachnoid hemorrhage. A histochemical and immunohisto-chemical study. J Neurosurg 65:531-539, 1986.

69 Hardebo JE, Hanko J, Owman CH: Species variation in the cerebrovascular response to neuro-transmitters and related vasoactive agents. Gen Pharmac 14:135-136, 1983.

70 Harper AM, Craigen L, Kazda S: Effect of the calcium antagonist, nimodipine, on cerebral blood flow and metabolism in the primate. J Cereb Blood Flow Metab 1:349-356, 1981.

71 Hartshorne DJ, Mrwa U: Regulation of smooth muscle actomyosin. Blood Vessels 19:1-18, 1982.

72 Heros RC, Zervas NT, Lavyne MH, Pickren KS: Reversal of experimental cerebral vasospasm by intravenous nitroprusside therapy. Surg Neurol 6:227-331, 1976.

73 Heros RC, Zervas NT, Varsos V: Cerebral Vasospasm after subarchnoid hemorrhage: An update. Ann Neurol 14:599-608, 1983.

74 Hirata Y, Matsukado Y, Fukumura A: Subarachnoid enhancement secondary to subarachnoid hemorrhage with special reference to the clinical significance and pathogenesis. Neurosurgery 11:367-371.

75 Holst von H, Granstrom E, Hammarstrom S, Samuelsson B, Steiner L: Effect of leucotrienes C_4, D_4, prostacyclin and thromboxane A_2 on isolated human cerebral arteries. Acta Neurochir 62:177-185, 1982.

76 Hughes JT, Schianchi PM: Cerebral artery spasm. A histological study at necropsy of the blood vessels in cases of subarachnoid hemorrhage. J Neurosurg 48:515-525, 1978.

77 Ishii R: Regional cerebral flow in patients with ruptured intracranial aneurysms. J Neurosurg 50:587-594, 1979.

78 Jackson FE, Back JB: Delayed arterial spasm and thrombosis as a cause of post-traumatic hemiplegia. Stroke 1:278-285, 1970.

79 Jaffe BM: The role of prostaglandins, in: Sabiston DC (ed): Textbook of Surgery. The Biological Basis of Modern Practice. Philadelphia, 1986, pp. 499-505.

80 Kapp JP, Neill WR, Neill CL, Hodges LR, Smith RR: The three phases of vasospasm. Surg Neurol 18:40-45, 1982.

81 Kassell NF: The natural history and treatment outcome of SAH: comments derived from the national cooperative aneurysm study, in: Battye (ed): Calcium Antagonists: Possible Therapeutic Use in Neurosurgery. New York: Raven Health Care Communications, 1983, pp. 24-29.

82 Kassell NF, Boarini DJ, Adams HP, Sahs AL, Graf CJ, Torner JC, Gerk MK: Overall management of ruptured aneurysm: Comparison of early and late operation. Neurosurgery 9:120-128, 1982.

83 Kassell NF, Drake CG: Timing of aneurysm surgery. Neurosurgery 10:514-519, 1982.

84 Kassell NF, Drake CG: Review of the management of saccular aneurysms. Neurol Clin N Amer 1:73-76, 1983.

85 Kassell NF, Peerless SJ, Drake CG: Cerebral vasospasm: acute proliferative vasculopathy? I. Hypothesis, in: Wilkins (ed): Cerebral Arterial Spasm. Baltimore: Williams & Wilkins, 1980, pp. 85-87.

86 Kassell NF, Peerless SJ, Drake CG, Boarini DJ, Adams HP: Treatment of ischemic deficits from cerebral vasospasm with high dose barbiturate therapy. Neurosurgery 7:593-597, 1980.

87 Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP: Treatment of ishemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. Neurosurgery 11:337-343, 1982.

88 Kassell NF, Torner JC, Adams HP: Antifibrinolytic therapy in the acute period following aneurysmal subarachnoid hemorrhage. Preliminary observations from the cooperative aneurysm study. J Neurosurg 61:225-230, 1984.

89 Kistler JP, Crowell RM, Davis KR, Heros R, Ojemann RG, Zervas N, Fisher CM: The relation of cerebral vasospasm to the exent and location of subarachnoid blood visualized by CT scan. A prospective study. Neurology 33:424-436, 1983.

90 Kosnik EJ, Hunt WE: Postoperative hypertension in the management of patients with intracranial arterial aneurysms. J Neurosurg 45:148-154, 1976.

91 Krueger C, Weir B, Nosko M, Cook D: Nimodipine and chronic vasospasm in monkeys. Part 2. Pharmacological studies of vessels in spasm. Neurosurgery 16:137-140, 1985.

92 Kudo T, Suzuki S, Iwabuchi T: Importance of monitoring the circulating blood volume in patients with cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery 9:514-520, 1981.

93 La Torre E, Patrono C, Fortuna A, Grossi-Belloni D: Role of prostaglandin F_2 in human cerebral vasospasm. J Neurosurg 41:293-299, 1974.

94 Levy WJ, Bay JW, Sawhny B, Tank T: Aminophylline plus nitroprusside and dopamine for treatment of cerebral vasospasm. A preliminary report. J Neurosurg 56:646-649, 1982.

95 Ljunggren B, Brandt L, Kagstrom E, Sundbarg G: Results of early operations for ruptured aneurysms. J Neurosurg 54:473-479, 1981.

96 Ljunggren B, Brandt L, Saveland H, Nilsson PE, Cronoqvist S, Andersson KE, Vinge E: Outcome in 60 consecutive patients treated with early aneurysm operation and intravenous nimodipine. J Neurosurg 61:864-873, 1984.

97 Lobato RD, Marin J, Salaices M, Burgos J, Rivilla F, Garcia AG: Effect of experimental subarachnoid hemorrhage on the adrnergic innervation of cerebral arteries. J Neurosurg 53:477-479, 1980.

98 Lobato RD, Marin J, Salaices M, Rivilla F, Burgos J: Cerebrovascular reactivity to noradrenaline and serotonin following experimental subarachnoid hemorrhage. J Neurosurg 53:480-485, 1980.

99 Locksley HB: Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section V, Part II. Natural history of subarachnoid hemorrhage, intracranial aneurysms, and arteriovenous malformations. Based on 6368 cases in the cooperative study. J Neurosurg 25:321-368, 1966.

100 Lye RH, Paul KS, Forster CM, Whalley ET, Dutton J: Effect of fibrin-fibrin degradation products on human basilar artery preparations. Possible role in the etiology of cerebral arterial spasm. J Neurosurg 56:339-343, 1982.

101 Lyons EL, Leeds NE: The angiographic demonstation of arterial vascular disease in purulent meningitis. Radiology 88:935-938, 1967.

102 Macpherson P, Graham DI: Arterial spasm and slowing of the cerebral circulation in the ischemia to head injury. J Neurol Neurosurg Psychiat 36:1069-1072, 1973

103 Maeda Y, Tani E, Miyamoto T: Prostaglandin metabolism in experimental cerebral vasospasm. J Neurosurg 55:779-785, 1981.

104 Marcus AJ, Broekman MJ, Weksler BB, Jaffe EA, Safier LB, Ullman HL, Islam N, Tack-Goldman K: Arachidonic acid metabolism in endothelial cells and platelets. Ann NY Sci 401:195-202, 1982.

105 Maroon JC, Nelson PB: Hypovolemia in patients with subarachnoid hemorrhage: Therapeutic implications. Neurosurgery 4:223-226, 1979.

106 Martin WRW, Baker RP, Grubb RL, Raichle ME: Cerebral blood volume, blood flow, and oxygen metabolism in cerebral ischemia and subarachnoid hemorrhage: An in vivo study using positron emission tomography. Acta Neruochir 70:3-9, 1984.

107 Matsumori K, Asahi S, Nakayama K, Miyasaka Y, Beppu T: Cerebral vasospasm following subarachnoid hemorrhage in arteriovenous malformation. No Shinkei Geka 11:829-839, 1983.

108 Mayberg MR, Houser W, Sundt TM: Ultrastructural changes in feline arterial endothelium following subarachnoid hemorrhage. J Neurosurg 48:49-57, 1978.

109 McCalden TA, Nath RG, Thiele K: The effects of a calcium antagonist (nimodipine) on basal cerebral blood flow and reactivity to various agonists. Stroke 15:527-532, 1984.

110 McCormick WF, Acosta-Rua GJ: The size of intracranial saccular aneurysms: An autopsy study. J Neurosurg 33:422-427, 1980.

111 Meyer FB, Anderson RF, Yaksh T, Sundt TM: Effect of nimodipine on intracellular brain pH, cortical blood flow, and EEG in experimental focal cerebral ischemia. J Neurosurg 64:617-626, 1986.

112 Mickey B, Vorstrup S, Voldby B, Lindewald H, Harmsen A, Lassen NA: Serial measurement of regional cerebral blood flow in patients with SAH using ^{133}Xe inhalation and emission computerized tomography. J Neurosurg 60:916-922, 1984.

113 Mizukami M, Kawase T, Usami T, Tazawa T: Prevention of vasospasm by early operation with removal of subarachnoid blood. Neurosurgery 10:301-307, 1982.

114 Mizukami M, Kin H, Araki G, Mihara H, Yoshida Y: Is angiographic spasm real spasm? Acta Neurochir 34:247-259, 1976.

115 Mizukami M, Takemae T, Tazawa T, Kawase T, Matsuzaki T: Value of computed tomography in the prediction of cerebral vasospasm after aneurysm rupture. Neurosurgery 7:583-586.

116 Montgomery EB, Grubb RL, Raichle ME: Cerebral hemodynamics and metabolism in postoperative cerebral vasospasm and treatment with hypertensive therapy. Ann Neurol 9:502-506, 1981.

117 Nakano M, Tani E, Fukumori T, Yokota M: Effects of chlorpromazine on experimental delayed cerebral vasospasm. J Neurosurg 61:857-863, 1984.

118 Norlen G, Olivecrona H: The treatment of aneurysms of the circle of Willis. J Neurosurg 10:404-415, 1953.

119 Noseworthy TW, Weir B, Boisvert D, Espinosa F, Overton T, Marshal ML: Effect of Reserpine-Kanamycin treatment on chronic vasospasm after platelet-enriched subarachnoid hemorrhage in primates. Neurosurgery 14:193-197, 1984.

120 Nosko MG: Studies in chronic cerebral vasospasm. PhD Thesis, University of Alberta, 1986.

121 Nosko M, Krueger CA, Weir BKA, Cook DA: Effects of nimodipine on in vitro contractility of cerebral arteries of dog, monkey, and man. J Neurosurg 65:376-381, 1986.

122 Nosko M, Norris SL, Weir B, King EG, Grace M: Nimodipine and chronic vasospasm in monkeys: Part 3. Cardiopulmonary effects. Neurosurgery 18:261-265, 1986.

123 Nosko M, Weir B, Krueger C, Cook D, Norris S, Overton T, Boisvert D: Nimodipine and chronic vasospasm in monkeys: Part 1. Clinical and radiological findings. Neurosurgery 16:129-136, 1985.

124 Nosko M, Weir B, Lunt A, Grace M, Allen P, Meilke B: Effect of clot removal at 24 hours on chronic vasospasm after SAH in the primate model. J Neurosurg 66:416-422, 1987.

125 Ohta T, Kikuchi H, Hashi K, Kudo Y: Nizofenone administration in the acute stage following subarachnoid hemorrhage. Results of a multi-center controlled double-blind clinical study. J Neurosurg 64:420-426, 1986.

126 Okwuasaba FK, Cook D, Weir B: Changes in vasoactive properties of blood products with time and attempted identification of the spasmogens. Stroke 12:775-780, 1981.

127 Okwuasaba FK, Weir BKA, Cook DA, Krueger CA: Effects of various intracranial fluids on smooth muscle. Neurosurgery 9:402-406, 1981.

128 Osaka K: Prolonged vasospasm produced by the breakdown products of erythrocytes. J Neurosurg 47:403-411, 1977.

129 Osterholm JL: Pathophysiological consequences of brain ischemia, in: Wilkins RH, Rengachary SS (eds): Neurosurgery. New York, McGraw-Hill, 1985, pp.1185-1188.

130 Otha H, Ito Z, Yasui N, Suzuki A: Extensive evacuation of subarachnoid clot for prevention of vasospasm...effective or not? Acta Neurochir(Wein) 63:111-116, 1982.

131 Ozaki N, Mullan S: Possible role of the erythrocyte in causing prolonged cerebral vasospasm. J Neurosurg 51:773-778, 1979.

132 Pang D, Sclabassi RJ, Horton Ja: Lysis of intraventricular blood clot with urokinase in a canine model: Part 2. In vivo safety study of intraventricular urokinase. Neurosurgery 19:547-552, 1986.

133 Pang D, Sclabassi RJ, Horton JA: Lysis of intraventricular blood clot with urokinase in a canine model: Part 3. Effects of intraventricular urokinase on clot lysis and posthemorrhagic hydrocephalus. Neurosurgery 19:553-572, 1986.

134 Paul KS, Whalley ET, Forster C, Lye R, Dutton J: Prostacyclin and cerebral vessel relaxation. J Neurosurg 57:334-340, 1982.

135 Peerless SJ: Postoperative cerebral vasospasm without subarachnoid hemorrhage, in: Wilkins (ed): Cerebral Arterial Spasm. Baltimore: Williams & Wilkins, 1980, pp. 496-498.

136 Peerless SJ, Griffiths JC: Plasma catecholamines following subarachnoid hemorrhage. Ann R Coll Phys Can 5:48-49, 1972.

137 Peterson JW, Adams JF, Zervas NT: Calmodulin antagonism can prevent and relieve delayed cerebral vasospasm in "two-hemorrhage" canine model. Circ 68(sup 3):171, 1983.

138 Peterson JW, Bun T, Candia GJ, Ronner SF, Charnvise K, Zervas NT: Basilar artery membrane is depolarized during cerebral vasospasm due to subarachnoid hemorrhage. Stroke 16:138, 1985.

139 Phillips LH, Whisnant JP, O'Fallon WM, Sundt TM: The unchanging pattern of subarachnoid hemorrhage in a community. Neurology 30:1034-1040, 1980.

140 Poppen JL: Symposium: Intracranial Vascular Abnormalities: Specific treatment of intracranial aneurysms; Experiences with 143 surgically treated patients. J Neurosurg 8:75-102, 1951.

141 Post KD, Flamm ES, Goodgold A, Ransohoff J: Ruptured intracranial aneurysms. Case morbidity and mortality. J Neurosurg 46:290-295, 1977.

142 Raynor RB, Messer HD: Severe vasospasm with an unruptured aneurysm: Case Report. Neurosurgery 6:92-95, 1980.

143 Robertson EG: Cerebral lesions due to intracranial aneurysms. Brain 72:150-185, 1949.

144 Rodriguez y Baena R, Gaetani P, Folco G, Branzoli U, Paoletti P: Cisternal and lumbar CSF concentration of arachidonate metabolites in vasospasm following subarachnoid hemorrhage from ruptured aneurysm: Biochemical and clinical considerations. Surg Neurol 24:428-432, 1985.

145 Ropper AH, Zervas NT: Outcome 1 year after SAH from cerebral aneurysm. Management morbidity, mortality, and functional status in 112 consecutive good-risk patients. J Neurosurg 60:909-915, 1984.

146 Rosenwasser RH, Delgado TE, Buchheit WA, Freed MH: Control of hypertension and prophylaxis against vasospasm in cases of subarachnoid hemorrhage: A preliminary report. Neurosurgery 12:658-661, 1983.

147 Rousseaux P, Scherpereel B, Bernard MH, Graftieaux JP, Guyot JF: Fever and cerebral vasospasm in ruptured intracranial aneurysms. Surg Neurol 14:459-465, 1980.

148 Saito I, Sano K: Vasospasm after aneurysm rupture. Incidence, onset, and course, in: Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore, 1980, pp. 294-301.

149 Sano K, Saito I: Timing and indication of surgery for ruptured intracranial aneurysm with regard to cerebral vasospasm. Acta Neurochir 41:49-60, 1978.

150 Sasaki T, Asano T, Takakura K, Sano K, Kassell NF: Nature of the vasoactive substance in CSF from patients with subarachnoid hemorrhage. J Neurosurg 60:1186-1191, 1984.

151 Sasaki T, Kassell NF, Yamashita M, Fujiwara S, Zuccarello M: Barrier disruption in the major cerebral arteries following experimental subarachnoid hemorrhage. J Neurosurg 63:433-440, 1985.

152 Saski T, Kassell NF, Zuccarello M, Nakagomi T, Fijiwara S, Colohan ART, Lehman M: Barrier disruption in the major cerebral arteries during the acute stage of experimental subarachnoid hemorrhage. Neurosurgery 19:177-184, 1986.

153 Sasaki T, Mayanagi Y, Yano H, Kim S: Cerebral vasospasm with subarachnoid hemorrhage from cerebral arteriovenous malformations. Surg Neurol 16:183-187, 1981.

154 Sasaki T, Murota S, Wakai S, Asano T, Sano K: Evaluation of prostaglandin biosynthetic activity in canine basilar artery following subarachnoid injection of blood. J Neurosurg 55:771-778, 1981.

155 Sasaki T, Tanishima T, Asano T, Mayanagi Y, Sano K: Significance of lipid peroxidation in the genesis of chronic vasospasm following rupture of an intracranial aneurysm. Acta Neurochir (Wein) Suppl 28, vol 2:536-540, 1979.

156 Sasaki T, Wakai S, Asano T, Takakura K, Sano K: Prevention of cerebral vasospasm after SAH with a thromboxane sythetase inhibitor, OKY-1581. J Neurosurg 57:74-82, 1982.

157 Sasaki T, Wakai S, Asano T, Watanabe T, Kirino T, Sano K: The effect of a lipid hydroperoxide of arachidonic acid on the canine basilar artery. An experimental study on cerebral vasospasm. J Neurosurg 54:357-365, 1981.

158 Saveland H, Ljunggren B, Brandt L, Messeter K: Delayed ischemic deterioration in patients with early aneurysm operation and intravenous nimodipine. Neurosurgery 18:146-150, 1986.

159 Schisano G: The use of antifibrinolytic drugs in aneurysmal subarachnoid hemorrhage. Surg Neurol 10:217-222, 1978.

160 Selman W, Spetzler R, Zabramski J: Induced barbiturate coma, in: Wilkins RH & Rengachary SS: Neurosurgery. New York, McGraw-Hill, 1985, pp. 343-349.

161 Shigeno T: Norepinephrine in cerebrospinal fluid of patients with cerebral vasospasm. J Neurosurg 56:344-349, 1982.

162 Shimizu K, Ohta T, Toda N: Evidence for greater susceptibility of isolated dog cerebral arteries to Ca antagonists than peripheral arteries. Stroke 11:261-266, 1980.

163 Simeone FA, Ryan KG, Cotter JR: Prolonged experimental cerebral vasospasm. J Neurosurg 29:357-366.

164 Smigiel MR, Sundt TM: Comparative effectiveness of alpha-blockade and beta-stimulation in modifying experimental basilar arterial spasm. J Neurosurg 41:300-334, 1974.

165 Solomon RA, Antunes JL, Chen RY, Bland L, Chien S: Decrease in cerebral blood flow in rats after experimental subarachnoid hemorrhage: a new animal model. Stroke 16:58-64.

166 Sonobe M, Suzuki J: Vasospasmogenic substance produced following subarachnoid hemorrhage, and its fate. Acta Neurochir 44:97-106, 1978.

167 Sundt TM, Onofrio BM, Merideth J: Treatment of cerebral vasospasm from subarachnoid hemorrhage with isoproterenol and lidocaine hydrochloride. J Neurosurg 38:557-561, 1973.

168 Suzuki J, Komatsu S, Sato T, Sakurai Y: Correlation between CT findings and subsequent development of cerebral infarction due to vasospasm in subarachnoid hemorrhage. Acta Neurochir 55:63-70, 1980.

169 Suzuki J, Onuma T, Yoshimoto T: Results of early operations on cerebral aneurysms. Surg Neurol 11:407-412, 1979.

170 Svendgaard NA, Edvinsson L, Owman CH, Sahlin CH: Increased sensitivity of the basilar artery to norepinephrine and 5-hydroxytryptamine following experimental subarachnoid hemorrhage. Surg Neurol 8:191-195, 1977.

171 Takagi T, Satake N, Shibata S: The inhibitory action of FR 34235 (a new Ca^{2+} entry blocker) as compared to nimodipine and nifedipine on the contractile response to norepinephrine, potassium, and 5-hydroxytryptamine in rabbit basilar artery. Eur J Pharmacol 90:297-299, 1983.

172 Takahashi S, Sonobe M, Nagamine Y: Early operation for ruptured intracranial aneurysms. Comparative study with computed tomography. Acta Neurochir 57:23-31, 1981.

173 Takayasu M, Suzuki Y, Shibuya M, Asano T, Kanamori M, Okada T, Kageyama N, Hidaka H: The effects of HA compound calcium antagonists on delayed vasospasm in dogs. J Neurosurg 65:80-85, 1986.

174 Tamura A, Asano T, Sano K: Protection from cerebral ischemia by a new imidazole derivative (Y-9179) and pentobarbital. A comparative study in chronic middle cerebral artery occlusion in cats. Stroke 10:126-134, 1979.

175 Taneda M: Effect of early operation for ruptured aneurysms on prevention of delayed ischemic symptoms. J Neurosurg 57:622-628, 1982.

176 Tani E, Maeda Y, Fukumori T, Nakano M, Kochi N, Morimura T, Yokota M, Matsumoto T: Effect of selective inhibitor of thromboxane A_2 synthetase on cerebral vasospasm after early surgery. J Neurosurg 61:24-29, 1984.

177 Tanishima T: Cerebral vasospasm: contractile activity of hemoglobin in isolated canine basilar arteries. J Neurosurg 53:787-793, 1980.

178 Tazawa T, Mizukami M, Kawase T, Usami T, Togashi O, Hyodo A, Eguchi T: Relationship between contrast enhancement on computed tomography and cerebral vasospasm in patients with subarachnoid hemorrhage. Neurosurgery 12:643-648.

179 Toda N: Mechanism of action of carbocyclic thromboxane A_2 and its interaction with prostaglandin I_2 and verapamil in isolated arteries. Circ Res 51:675-682, 1982.

180 Toda N: Alpha adrenergic receptor subtype in human, monkey, and dog cerebral arteries. J Pharmacol Exp Ther 226:861-868, 1983.

181 Toda N, Ozaki T, Ohta T: Cerebrovascular sensitivity to vasoconstricting agents induced by subarachnoid hemorrhage and vasospasm in dogs. J Neurosurg 46:296-303, 1977.

182 Varsos VG, Liszczak TM, Han DE, Kistler JP, Vielma J, Black PM, Heros RC, Zervas NT: Delayed cerebral vasospasm is not reversible by aminophylline, nifedipine, or papaverine in a "two-hemorrhage" canine model. J Neurosurg 58:11-17, 1983.

183 Voldby B, Engbaek F, Enevoldsen EM: CSF serotonin concentrations and cerebral arterial spasm in patients with ruptured intracranial aneurysm. Stroke 13:184-189, 1982.

184 Weir B: Calcium antagonists, cerebral ischemia and vasospasm. Can J Neurol Sci 11:239-246, 1984.

185 Weir B, Aronyk K: Management mortality and the timing of surgery for supratentorial aneurysms. J Neurosurg 54:146-150, 1981.

186 Weir B, Grace G, Hansen J, Rothberg C: Time course of vasospasm in man. J Neurosurg 48:173-178, 1978.

187 Weiss GB: New perspectives on calcium antagonists. American Physiological Society, Bethesda. Baltimore: Williams & Wilkins, 1981.

188 Wellum GR, Irvine TW, Zervas NT: Dose responses of cerebral arteries of the dog, rabbit, and man to human hemoglobin in vitro. J Neurosurg 53:486-490, 1980.

189 Wellum GR, Irvine TW, Zervas NT: Cerebral vasoactivity of heme proteins in vitro. Some mechanistic considerations. J Neurosurg 56:777-783, 1982.

190 White RP, Chapleau CE, Dugdale M, Robertson JT: Cerebral arterial contractions induced by human and bovine thrombin. Stroke 11:363-368, 1980.

191 White RP, Cunningham MP, Robertson JT: Effect of the calcium antagonist nimodipine on contractile responses of isolated canine basilar arteries induced by serotonin, prostaglandin F_2, thrombin, and whole blood. Neurosurgery 10:344-348, 1982.

192 White RP, Heaton JA, Denton IC: Pharmacological comparison of prostaglandin F_2, serotonin and norepinephrine on cerebrovascular tone of monkey. Eur J Pharmacol 15:300-309, 1971.

193 White RP, Robertson JT: Comparison of piroxicam, meclofenamate, ibuprofen, aspirin, and prostacyclin efficacy in a chronic model of cerebral vasospasm. Neurosurgery 12:40-46, 1983.

194 White RP, Robertson JT: Role of plasmin, thrombin, and antithrombin III as etiological factors in delayed cerebral vasospasm. Neurosurgery 16:27-35, 1985.

195 Wilkins RH: Attempted prevention or treatment of intracranial arterial spasm: A survey, in: Wilkins RH (ed): Cerebral Arterial Spasm. Baltimore: Williams & Wilkins, 1980, pp. 542-555.

196 Yamakami I, Isobe K, Yamaura A, Nakamura T, Makino H: Vasospasm and regional cerebral blood flow (rCBF) in patients with ruptured intracranial aneurysm: serial rCBF studies with Xenon-133 inhalation method. Neurosurgery 13:394-401.

197 Yamamoto YL, Feindel W, Wolfe LS, Katoh H, Hodge CP: Experimental vasoconstriction of cerebral arteries by prostaglandins. J Neurosurg 37:385-397, 1972.

198 Yoshida Y, Ueki S, Takahashi A, Takagi H, Torigoe H, Kudo S: Intrathecal irrigation with urokinase in ruptured cerebral aneurysm cases. Basic study and clinical application. Neurol Med Chir (Tokyo) 25:989-997, 1985.

199 Yashon D, Brown RJ, Hunt WE: Vasoactive properties of prostaglandin compounds on the in vitro human basilar artery. Surg Neurol 8:111-115, 1977.

200 Young HA, Kolbeck RC, Schmidek HH: Hemorrhage-induced alterations of rabbit basilar artery reactivity and sensitivity to serotonin. Neurosurgery 19:502-506, 1986.

201 Zabramski JM, Spetzler RF, Bonstelle C: Chronic cerebral vasospasm: Effect of volume and timing of hemorrhage in a canine model. Neurosurgery 18:1-6, 1986.

202 Zabramski JM, Spetzler RF, Bonstelle C: Chronic cerebral vasospasm: Effect of calcium antagonists. Neurosurgery 18:129-135, 1986.

203 Zervas NT, Hori H, Rosoff CB: Experimental inhibition of serotonin by antibiotic: prevention of cerebral vasospasm. J Neurosurg 41:59-63, 1974.

204 Zervas NT, Liszczak TM, Mayberg MR, Black PM: Cerebrospinal fluid may nourish cerebral vessels through pathways in the adventitia that may be analogous to systemic vasa vasorum. J Neurosurg 56:475-481, 1982.

PUBLICATIONS

1. Lewis PJ, Noseworthy TW, Fitzgerald AA, Andrews GC, Geeraert AJ: Rapid reversal of ergotamine-induced vasospasm. Can J Neurol Sci 13:72-74, 1986.

2. Lewis PJ, Weir BK, Broad RW, Grace MG: Long-term prospective study of lumbosacral discectomy. J Neurosurg 67:49-53, 1987.

3. Lewis PJ, Weir BK, Nosko MG, Tanabe T, Grace MG: Intrathecal nimodipine therapy in a primate model of chronic cerebral vasospasm. Submitted for publication.